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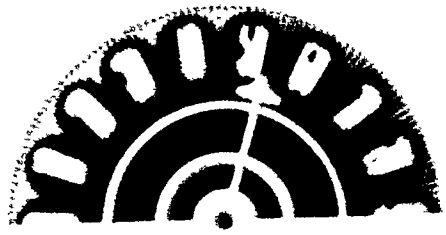
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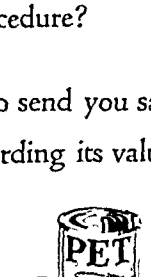
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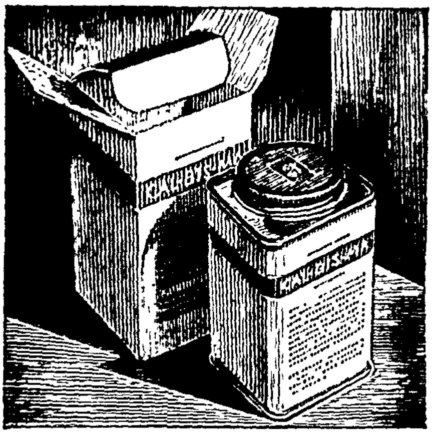
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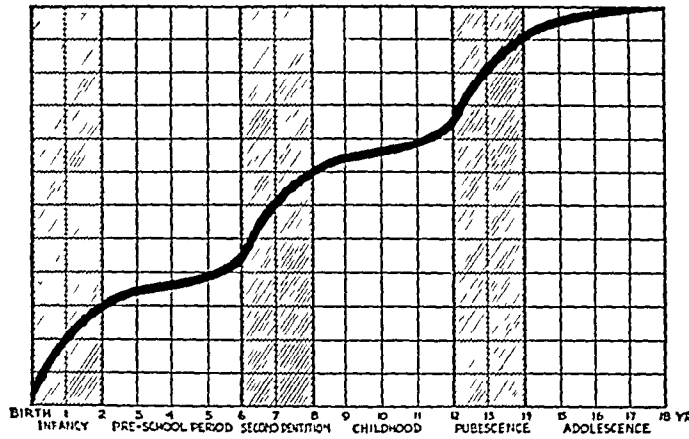
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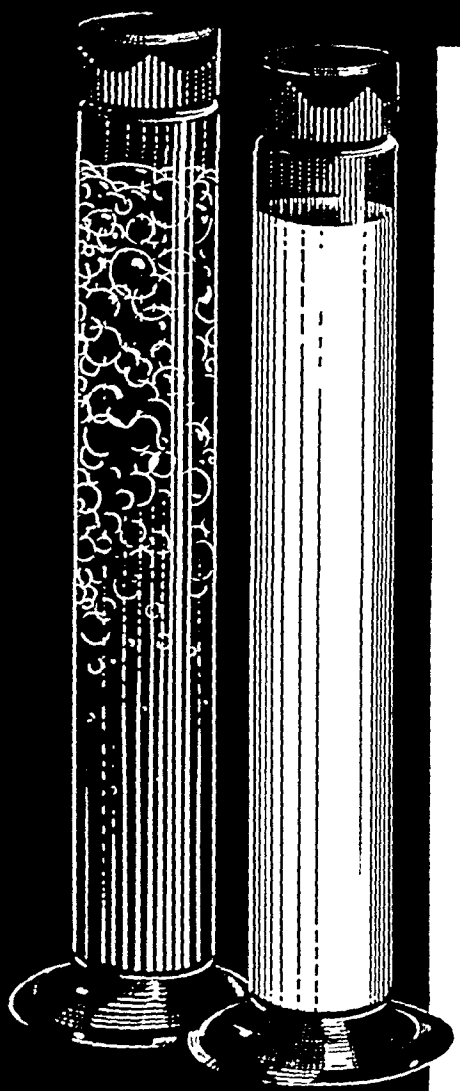
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VITAMINS IN CANNED FOODS

III. VITAMIN A

• The most characteristic evidence of severe human vitamin A deficiency, and one which is increasingly rare in this country, is xerophthalmia. Night-blindness, one of the manifestations that usually precedes xerophthalmia, has been recognized as a deficiency disease since the time of Hippocrates who described the disease, and its cure by eating liver. Infrequent reports of this disorder, however, still appear in the American literature. Most if not all of the symptoms accompanying a deficiency of vitamin A are thought to be the result of an impairment of the epithelial tissue (1). In this connection, a new method for the quantitative determination of this vitamin is based on the keratinization of germinal epithelia (2).

That vitamin A exerts an influence on the growth of human infants and children is also generally accepted.

As early as 1919, a relationship between vitamin A in plant foods and plant pigments was postulated. Research since that date has indicated that beta-carotene and some related compounds may be considered as provitamin A (3).

The vitamin A potency of fruits and vegetables is apparently due to their carotene content, since vitamin A as such has never been found in plant tissue. Ingested carotene is believed to be converted into vitamin A by enzyme action in the liver of the animal (4), in which organ the vitamin is stored.

Vitamin A in the form of carotene may be present in yellow, green or red pigmented fruits and vegetables—in the two latter cases, the yellow color of carotene being masked by other pigments present. Color alone, therefore, is not always a reliable index of potential vitamin A potency.

Both vitamin A and carotene are relatively stable to heat but are subject to destruction by oxidation. However, foods of both animal and plant origin, when canned by modern methods, have been found to retain their vitamin A potencies in high degree (5).

In fact, in some instances, practically no loss of vitamin A potency can be detected by formal bio-assays (6).

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1 a 1927 J Exp Med, 46, 709
2 1933 J Nutrition, 9, 535
3 1922 J Biol Chem, 51, 377
(4) 1931 J Biol Chem, 94, 165
5 a 1933 J Am Dietet Assoc, 9, 235
b 1931 J Nutrition, 4, 267
c 1935 Am J Pub Health, 25, 1349
(6) a 1925 Ind Eng Chem, 17, 69
b 1926 Ind Eng Chem, 18, 85

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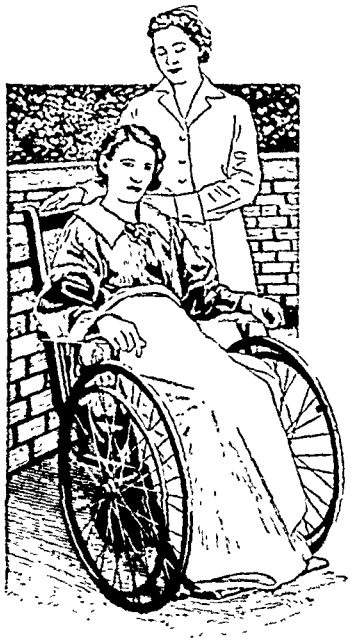
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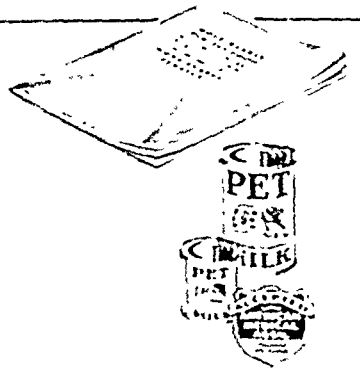
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The Official Publication of
THE AMERICAN GASTRO-ENTEROLOGICAL ASSOCIATION

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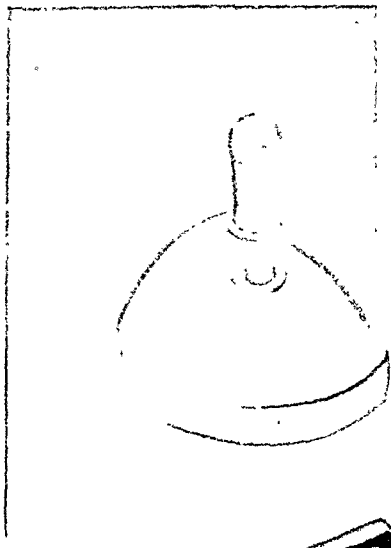
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SECTION I—*Clinical Medicine: Diseases of Digestion*

Personality Study in Cardiospasm: The Meaning of the Disorder From the Standpoint of Behavior*

By

EDWARD WEISS, M.D.†

PHILADELPHIA, PENNSYLVANIA

PREVAILING opinion in regard to psychic factors in the etiology of cardiospasm may be stated as follows: (1) that the disorder is a physical one and psychic factors are considered of no importance or are unnoticed; (2) that it is a disorder of physical origin in which psychic factors are frequently found which are probably secondary to the physical disorder; (3) that it is a physical disorder in which psychic factors are present because these individuals are subjects with autonomic imbalance, that is, vagotonics, in whom physical disorders of the vegetative nervous system and psychological difficulties are apt to coexist; (4) that in some way psychic factors, acting through the vegetative nervous system, are specifically responsible for the cardiospasm.

These viewpoints are not so very different from current attitudes in regard to the other numerous functional disorders of the gastro-intestinal tract, and indeed, for our purposes, cardiospasm may be said to constitute only one small phase of this larger problem which is so badly in need of solution. The question of cardiospasm may be said to have an even greater implication, in that it touches upon the great border-line problem of the interrelationship of physical and psychological disease. For if evidence were forthcoming in favor of the psychogenic origin of even some cases of cardiospasm it would aid in the establishment of the important concept of the role of psychogenesis in the determination of structural disease, a field of medical investigation that is just beginning to be studied.

In order to develop this point let me suggest that the concept of disease bequeathed to us by nineteenth century medicine could be expressed in the following formula:

cellular disease — structural alteration — functional (physiological) disturbance.

The development of this concept represented an about-face from the medical ideas of the period of the priest—physician who was especially concerned with the spiritual basis of illness. With the introduction of the structural concept of disease by Virchow there occurred a separation of illness from the *psyche* of man and a consideration of disease as only a disorder of organs and cells. With this separation of disease into many different ailments came the development of specialists to attend to all of these distinct diseases. With the specialist came the introduction of instruments of precision and the mechanization of medicine began. Medicine then contented itself with the study of the organism as a physiological mechanism, impressed by blood chemistry, electrocardiography, etc., but unimpressed and, indeed, often holding in contempt the psychological background of the individual which was not considered as scientific as the result of laboratory studies. This period may, in truth, be referred to as the "machine age in medicine." It is not to be denied that remarkable developments have occurred during this period of laboratory ascendency but it also must be admitted that the emotional side of illness has been almost entirely neglected. As a consequence there has been a lack of insight into the emotional problems and accompanying organ dysfunctions of the sick individual.

Since the turn of the century, however, physicians have begun to recognize that cellular disease may be preceded by long-continued functional disturbance: witness, for example, the development of this conception, during this period, in regard to the disorder of essential hypertension and vascular disease. Under certain circumstances, therefore, the formula of disease could then be altered to read:

functional disturbance — cellular disease — structural alteration.

We are still in the dark as to what may precede the functional disturbance, as in the example just cited of essential hypertension and resulting vascular disease. May it not be that future investigations will permit us, in some cases at least, to say that it is possible, among other causes, for a psychological disturbance to antedate the functional alteration. Then, in some instances, the formula would read:

psychological disturbance — functional impairment — cellular disease — structural alteration.

I do not think it is necessary to point out that psychic factors, acting through the vegetative nervous system, can affect the function of various parts of the gastro-intestinal tract. Cannon, in his noteworthy experiments, proved that point many years ago and we have familiar daily examples of vomiting, diarrhea,

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Approved by the Publications' Committee of the Association.

†Professor of Clinical Medicine, Temple University School of Medicine.

etc., directly traceable to forceful emotional influences. What is not so generally accepted, however, is that long continued (chronic) disturbances of a physiologic nature can also be due to psychological influences. The very fact that these powerful psychological influences are of *unconscious origin* explains their persistent effect and also the fact that they are not well understood generally.

The present study is not concerned with the pathogenesis of cardiospasm. Nor does it pretend to be an exhaustive psychological study. It is only an effort to enter a little more thoroughly into the emotional lives of patients with cardiospasm, than previously reported cases indicates has been done, in an attempt to see if some meaning for the disorder can be found from the standpoint of behavior.

The following cases have been selected from a group referred to me for general medical study through the kindness of Dr. C. L. Jackson of the Bronchoscopic department, Temple University Hospital. His own views on the subject have been published recently (1).

AUTHOR'S STUDIES

Case I. An unmarried school teacher, aged 30, complained of stomach trouble and swallowing difficulty, of about 6 months' duration. She always had been constipated but had had no previous serious illness. She had lost 28 pounds since the onset of the present illness. Other than the poor nutrition, physical examination was negative. Esophagoscopy and X-ray showed cardiospasm but no dilatation of the esophagus. In treating the patient Dr. C. L. Jackson found that she did not tolerate the dilator well but it was felt that there had been some response to dilatation and *the patient wanted treatment.*

LIFE SITUATION

The patient was a middle child in a large family the medical history of which threw no light on the patient's illness. The family is described as a religious one and two sisters married ministers. The patient states that she was a normal child; that she had had no behavior difficulties except an occasional nightmare.

Menses was established at 14; periods were always regular and never associated with pain until recently. She attended normal school and college, fitting herself as a teacher. She then obtained a position as a high school teacher in another city and developed many cultural interests in addition to her teaching. She was a very industrious person seeking constantly to improve herself and widen her outlook.

She was not interested in boys, nor did she develop any such interest until she went to college. She grew up with the idea that it was improper for parents to have intercourse except for the purpose of having a family.

Several years ago she began to receive attentions from another teacher in the school, a man thirteen years her senior, who had separated from his wife and was about to obtain a divorce. Even before his divorce was granted, he suggested marriage but her family objected. This took place in the summer three years ago and she recalls that she suffered some indigestion coincident with the receipt of the letter from her family objecting to the proposal. Subsequently he frequently suggested marriage but for one reason or another she has held off. The reasons stated by the patient do not seem satisfactory for this long postponement of marriage. During this period her suitor was persuading her to have intercourse on the basis that it was a necessary test for marriage. The patient had no sexual desire and had many moral scruples against intercourse. However, she gradually overcame them and finally submitted but with great fear of becoming pregnant. About the same time she developed dysmenorrhea and had one rather severely painful period. She also noted an increasing irritability. A menstrual period began on February 8, 1933, but stopped two days later and she promptly considered herself pregnant and with this a severe attack of indigestion began. The indigestion was immediately followed by difficulty in swallowing. She entered a hospital and remained about three weeks without benefit. So great was her fear that in spite of the fact that her menses returned she continued to believe herself pregnant, suffered from morning nausea and vomiting and stated that her abdomen was swollen and hard "just as though there was a baby inside." In April her physician stated that he would have to make a gynecologic examination and this exaggerated her fear of pregnancy. He did not do so, however, and gradually her fear left. During this whole period she had many arguments with her suitor and at times felt that she would lose him and this, of course, added to the humilation of the supposed pregnancy. On one occasion he was supposed to visit her but wrote saying that he would have to postpone his visit. Immediately she had an exacerbation of her swallowing trouble. And it was just following this episode that Dr. C. L. Jackson reported, after an attempted treatment, "the esophagus failed to relax; the crico-pharyngeal pinch-cock was tightly closed. The patient does not tolerate the dilator well." Now, in addition, each menstrual period was associated with an increase in swallowing trouble.

The picture we get is that of a sexually inhibited (frigid) girl who had great difficulty in bringing herself to marry, maintaining a long engagement, finally yielding to intercourse, probably persuaded by the threat of losing her man whom she was afraid to marry and afraid to lose. Finally her guilty feelings culminated in an ill-founded idea that she was pregnant, because of a disturbance in her menstrual period, and then indigestion and swallowing difficulty occurred and presisted. So exaggerated was her fear of pregnancy that it was maintained in spite of subsequent menstrual periods, and thus we obtain some insight to the degree of fear and how powerful its influence might be in affecting the functions of her body.

In this case, therefore, cardiospasm occurred in a young woman with repressed sexuality in whom an obvious and easily ascertained conflict over marriage and sexual transgression seemed to act as the precipitating factor.

It is not at all unusual for young women to influence their menstrual periods by emotional disturbances arising in connection with the idea of pregnancy, but it is unusual for the fear and guilty feelings to be as pronounced as in this patient. This could only occur in a person with pronounced sexual inhibitions. Apparently this sexual transgression, which would not have provoked such symptoms in an average girl, called for an unusual degree of self-punishment in this patient.

It might be stated at this point that disturbance in sexuality is not the cause of neurosis but simply serves

as an index to a neurotic personality. There has been much misunderstanding on this question. In personality study sexual difficulties, such as impotence and premature ejaculation in the male and frigidity of various degrees in the female, serve as clues to the kind of a personality that is very liable to develop a neurosis. They, themselves, are not the cause of the neurotic difficulty.

In the next patient the problem was not quite so obvious and called for more insight into unconscious mental forces so that the conflict, of which the patient was unaware, could be detected.

Case II. A white girl of 19, was first seen in July, 1933. The cardiospasm, with evidence of some esophageal dilatation, was of three years duration. The previous medical history did not seem important in relation to the cardiospasm.

LIFE SITUATION

The patient described herself as a spoiled child (because she was an only child until the age of 12), who suffered from temper tantrums but did well in school. She is devoted to her father but does not get along well with her mother who, she says, possesses a bad temper. She is strongly under the influence of her very religious father who has had difficulty in declaring his allegiance to any one church because of his failure to find complete satisfaction there. At the age of ten she was sent to the Sunday School of the religious organization to which her father became a new adherent. She can recall even at this early age attending a revival meeting and subsequently having religious doubts about her own "feelings." Already she possessed the ambition to come a missionary. All through high school she had grave doubts of a religious nature. Then, during her senior year she was unable to decide what college to attend. She wanted to go to some "modern" school but feared that it would possess a "jazz" spirit and this was at variance with her religious belief which was, to forsake worldly pleasures, such as dancing, cards and the theatre.

About this time her father brought her difficulties to a climax by talking to her "on the necessity of becoming a true Christian—she had become old enough, 16." She was terror stricken by her father's conclusion and pretended, by reading a book, that she did not hear what he was saying. It was at this time that her swallowing difficulty first appeared.

She finally chose a conservative college but while there a very severe attack of swallowing difficulty occurred in connection with the idea of engaging in college dramatics to which she had been very devoted. Her reason was rather fanciful but none the less valid (as easily was apparent from her attitude in our discussion) that is, she feared that if she became successful in dramatics it would offer her the additional temptation of a successful stage career. And so she thought "I cannot take a chance on becoming a dramatic success, then I could not be a Christian." The situation was the same as before, that is, a conflict between freedom and the straight and narrow path of her (and her father's) religious beliefs.

In this case cardiospasm arose in a girl with a pronounced emotional conflict over the question of religion. The swallowing difficulty occurred when the conflict was at its height and was exacerbated when further psychic situations touched her emotional problem. She told me that shortly after she developed the illness she thought that she could resign herself to it "because it was intended by the Lord." She looked upon the illness as something outside of herself, for which she was in no way responsible, and felt quite hopeless about treatment. She thought the disorder would disappear "when He willed it so." She was very touchy on this religious question and resented any implication that a conflict existed in her and that her swallowing difficulty was the answer to that conflict. For it would seem that the symptom served several purposes. As she, herself, expressed it "it served the useful purpose of keeping her away from a 'jazz' school and led her into the proper path of the true religious faith." At the same time it was a protest against the harshness of this straight and narrow path and was also the inner revolt of a mild and passive creature against the father's religious fanaticism. More than that it punished her for thoughts of digression but, at the same time, succeeded in evoking her father's sympathy, whose devotion she so much desired.

The father, too, considered his daughter's condition "beyond human help." Nevertheless, he continued to send her for treatment and constantly sought advice and opinion regarding her condition.

It also must be apparent, from her resigned attitude toward the illness and the purposes that it seemed to serve, that mechanical treatment alone could hardly hope for success. Indeed, so necessary did the illness appear to be for a partially satisfactory adjustment of her emotional life that to take it away without preparing her psychologically might have resulted in its being replaced by a more serious condition, as apparently happened in another case.

In passing, it might be remarked that the religious question has frequently served to focus anxiety and thus precipitate a neurotic illness in adolescents who have neurotic tendencies.

Case III.* A white man of 55, first seen in February, 1933, showed marked cardiospasm and pronounced esophageal dilatation.

The patient gave the usual medical history of this condition. He stated that his illness began about 8 or 10 years before and had become progressive. He had consulted many physicians. Discouraged, he had invested a large sum of money with an osteopath who had promised cure. Finally, when very sick and without funds he had come to the hospital. The previous medical history did not seem to bear upon this illness.

LIFE SITUATION

The patient had been "born into the drug business" and had never known anything except the long hours and tedious work of an under-paid pharmacy clerk. He married young and five children came in rapid succession. It was a great financial struggle to look after them. About 1916 or 17 while working very hard he had "some kind of a nervous breakdown" which lasted several weeks. In 1922 his oldest and favorite son, then age 20, had just obtained an excellent job which paid well. He gave his salary to his mother and the father was overjoyed with the finally achieved prospects of economic freedom. He had always pictured a great career for this able son and had looked forward to his financial aid in old age.

Without warning one morning shortly afterward he

*Previously published (2) as one of the cases illustrating the necessity for personality study in the practice of internal medicine.

learned that this son had secretely married. He said "It was the greatest blow I ever received, not only because of the financial part of it but the way he did it." The patient placed his hand in his epigastrium to show where he had felt the blow.

He could not get over this disappointment and even considered having the marriage annulled on the basis that the boy was too young to marry. It is interesting to note, however, that he, himself, had married at the same age. He harbored a great deal of resentment for the girl's parents who, he felt, had stolen his fine son from him. It was during this period that attacks of swallowing difficulty occurred and grew more pronounced and more frequent.

A short time later further aggravation occurred. He learned that his brother in England, whom he described as a ne'er-do-well, was cheating his mother of her small legacy. He went to England, brought his mother back and she now makes her home with him. It is significant that the mother contributes her whole income to the up-keep of him and his family. In other words, while he accuses his brother of having "bled his mother" he, himself, had already borrowed money from her and now takes her weekly allowance for living expenses. His altruism in rescuing her from his ne'er-do-well brother seems questionable.

The picture we get is that of a meek, submissive and dependent individual who had always worked hard without achieving success, strongly identified with his oldest son in whom he hoped to achieve the success denied himself. With his son's secret marriage came a tremendous disappointment from which he could not recover.

An interesting commentary in line with my thesis is his experience with the osteopath. He consulted him about December, 1931, and was charged $1,000 "for the management of his case," which his sons had to borrow. It is interesting to consider why he felt like investing this great sum of money with the osteopath. He says "the osteopath told me that my trouble was due to a spasm arising from a shock" and the patient went on to say to me "he did not know about my son's marriage." He was much impressed by this diagnosis "because it was the first time that any doctor had suggested that shock and worry might be responsible for my trouble." He thereupon placed his entire confidence and all the money that he could raise in the osteopath's hands.

In the recital to me, accompanied by great emotion, this poor druggist made the following significant and perhaps revealing statement. "My son's marriage was a bitter pill that I could not swallow." And who can say that that was not, at least, one meaning of the illness?

For it would seem, from the resentment with which he speaks of his son's "treachery," that the aggression which this meek and dependent creature would like to express against his son, but cannot because of his attachment to him, is turned against himself. However, it is interesting to observe, as frequently happens in neurotic individuals, that this illness does accomplish the purpose of making him dependent upon his son (and mother) as he had been in phantasy. And thus, he actually punishes them as well as himself.

The fourth case has a deep psychic conflict with pronounced evidences of physiological disturbance in more than one system.

Case IV. A young white man of thirty, first seen in July, 1933, complained of difficulty in swallowing and vasomotor rhinitis. Esophagoscopy and X-ray showed pronounced cardiospasm with a greatly dilated esophagus. The swallowing difficulties had begun many years before (in puberty) and had continued intermittently for several years with a severe attack about the age of seventeen. In recent years his difficulties have been very persistent.

LIFE SITUATION

The patient was an only child who describes his father as a quiet, plain person, much older than the patient's very excitable mother. The parents never got along well and separated for a period when the patient was about six years old.

His earliest recollections of himself concern attacks of fever as a child, the mother taking his rectal temperature and frequently annoying him by putting her fingers down the back of his neck to test the temperature. He also states that he had a nervous habit of chewing the pages of the books that he read.

About the age of 14 while travelling with his mother she gave him an apple, a piece of which he had difficulty in swallowing. He asked for a drink and she said, "why do you pretend that you cannot swallow the apple when you only want a drink." This attitude of her's he considered very characteristic. And his reaction to his mother has constantly been an antagonistic one. He considers his mother "a neurotic who had temper tantrums and took them out on me." He recalls that riding on the train at about this time aggravated his swallowing symptoms. At 17 he went away to school where he was very unhappy. He had a nervous breakdown and was in a sanitarium for 5 weeks. His mother then came to spend a vacation with him and they went to a high altitude together after a bad night of travel. According to the patient there was a combination of fatigue, mental depression, the high altitude and the presence of his mother. And all together he holds them responsible for a severe attack of swallowing difficulty, so that he could not get any food or even liquid down. He was rushed to a nearby city where X-ray studies were made and a diagnosis of esophageal obstruction established. From then on various treatments were attempted directed to his esophagus—gastric lavage, passing of sounds and exhibition of atropin.

Frequently during his early years he suffered from what he called bronchitis and then in 1931 the attacks seemed to be replaced by vasomotor rhinitis.

During his adolescence he was constantly disturbed by sexual worries of one nature or another (masturbation) (and on two occasions homosexual experiences) and at about the age of 24 attempted intercourse with an older woman but suffered premature ejaculation. After frequent attempts of intercourse and constant failure he consulted a genito-urinary specialist who treated him by massage of his prostate and the insertion of sounds. He constantly broods about his sexual life and gives the impression that his whole life, from puberty on, has been devoted to the purpose of accomplishing sexual intercourse successfully. Relatively speaking he seems little concerned about his esophagus. What does tremendously concern him is his impotence which he speaks of as his "sexual weakness." So profoundly is he affected that he has little energy left for his job and performs routine duties in

a very perfunctory way. He seems as little concerned about the job as he is about his esophagus. The life-long disturbed relationship to the mother, the difficulties in the sexual sphere, the lack of ambition in his job despite a good intelligence, and his unhealthy relationship to men in general are certain indications of a neurotic personality.

The conflict thus is seen to be of deeply rooted origin and seems to manifest itself in several different systems, respiratory (vasomotor rhinitis), gastro-intestinal (cardiospasm) and genital (impotence) as well as in the total personality. The specific psychic meaning of the various physical disorders is not clear but it must be apparent that to treat the cardiospasm simply by mechanical dilatation would be just as short of complete medical management as was the passing of sounds in the treatment of the impotence.

In the last case the emotional conflict became apparent only through a chance discovery.

Case V. A white girl, aged 15, had swallowing difficulty which began about a year and a half ago. Just prior to this she had had some dental work done and complained of a curious sensation of the teeth which also preceded the attack of swallowing difficulty. The attacks are accompanied by pain in the chest and salivation. Esophagoscopy and X-ray demonstrate cardiospasm with dilatation of the esophagus.

LIFE SITUATION

The patient, the youngest child of a family of five, was always in good health until the present trouble began. She suffered from enuresis as an infant and also from night terrors, and formerly was afraid of the dark, imagining a burglar to be in the house. Menses began a year before the onset of the trouble and were always regular. Frequent conversation failed to bring out any emotional occurrences that seemed significant in regard to her trouble. It is true that the financial situation was bad at home and that the mother was at times ill but neither situation seemed important in relationship to her illness. She gave the impression in her frequent interviews of being a very straight-laced young lady, interested in boys but very mindful of the dangerous possibilities of being associated with them and determined to protect herself. After many efforts to discover the cause of her trouble, quite by accident her mother came to me suffering from a functional gastro-intestinal disorder and told a story which probably had to do with her own illness as well as with the patient of whom I am speaking.

The patient has a sister 12 years older than she who has been a source of great trouble to the family. At the age of 10 this sister began having difficulties at school with truancy and false reports. At 16 she ran away from home (when our patient was 4) was brought back and ran away again at 17 and this time when she returned was illegitimately pregnant and had a child which was disposed of through an agency. The patient was aware of the fact that this sister had had an illegitimate child; she had heard her mother describe it. Still later the sister married, out of her faith, had another child and just prior to the onset of our patient's illness was being sued for divorce and had returned to her home.

It was then possible to correlate this story with the swallowing problem of our patient who, even as a small child, was well aware of the disgrace to her family, was very much concerned that nobody in the neighborhood should know of the trouble, and whose swallowing difficulty began about the time that she learned of the divorce action. A divorce, of course, meant that the bad sister would be thrown upon their hands again and endanger their prestige in the neighborhood. This coincided with the period of puberty, when, because of tremendous psycho-physical development, emotional disturbances and their physical consequences are most apt to arise. The whole situation certainly would appear to have something to do with the severe repression of our patient. She, herself, says that her sister's trouble was due to bad companions. In this connection a dream of our patient is interesting: "she was standing between two girls who fell down and blamed her." Falling down is a well known symbol for a moral fall and is over-determined in the dream. Regardless of any further meaning that the dream may have it indicates the thoughts with which the patient was concerned and from which conflict arose.

The cardiospasm apparently indicates the inability of the patient "to swallow" the family disgrace. It must be emphasized that no conscious worries could be ascertained by the simple question, "are you worried about anything?" Indeed, if the mother had not given me the story of the older daughter I do not think that, in the time at my disposal, I could have worked out this girl's important problem.

DISCUSSION

In these cases of cardiospasm, and others that I have studied, the disorder seems to have a special meaning in terms of behavior. This meaning can be discovered by a study of the personality in relation to the environment. The cardiospasm often is found to arise coincidently with an emotional conflict, in many instances during puberty, in an individual whose early life gives evidence of personality difficulties. At first the disorder frequently seems to manifest itself intermittently; later on, it may become persistently established. Exacerbations occur which, frequently, can be correlated with fresh psychic insults touching the particular complex of the individual.

In this respect, it is worthy of comment, that one may note in papers on cardiospasm statements such as "the patient did not look neurotic" or "the patient wasn't worried about anything." Unfortunately for us, most such patients do not betray their neuroses by their appearance nor is the simple question "are you worried about anything?" likely to produce material of importance. In some instances (as in Case I) the conflict is fairly obvious but in others insight into unconscious mental mechanisms is necessary in order to discover a deep conflict of which the patient may be totally unaware.

It would seem then, as stated above, that the cases cited correspond in all respects to conversion hysteria of a form deeply rooted in the unconscious mental life of the individual. The physical disorder represents symbolically the unconscious conflict—it appears to be a compromise between the gratification of certain forbidden impulses and their rejection by another part of the personality. An important meaning of the disorder often can be stated in such simple terms as "I can't swallow that (situation)." Therefore, this meaning often can be discovered by looking (psychologically) for the situation that the individual "cannot swallow."

This kind of information furnishes a specific back-

ground for the cardiospasm and replaces the loose terminology and loose thinking behind such terms as "nervous factors" and "neurogenic background" with a more exact definition of the specific psychic situation. Indeed, to speak of "nervous factors" in the back-ground of the patient with cardiospasm without further defining them seems to me as obsolete as blaming malaria on marsh gas with failure to note the part played by the malarial parasite. In self-criticism, I may say that I have not found the parasite but I do think that I have the mosquito.

I must emphasize that I do not believe that the psychic situation is the only one of importance in these cases of cardiospasm. The physiological mechanism of cardiospasm has not been discussed nor has any consideration been given to the question of the differentiation between intermittent and persistent forms with dilatation of the esophagus. Thieding (3), Vinson (4) and others make this differentiation but I did not concern myself with the question at this time. I must content myself, for the present, with the observation that psychologically, in my experiences, both have arisen out of similar situations. Nor have I discussed esophagitis in association with cardiospasm. Is it, as Lyon (5), and others have suggested, a result of the purely functional lesion that, once established, predisposes to further spasm? From the psychic standpoint, other questions have not been discussed. Why should the psychic situation affect the gastro-intestinal tract, and that particular portion of it, and why should the situation produce the illness in certain people and not in others? These are some of the questions upon which one could speculate but I prefer to await further physical and psychological studies aimed at the deeper levels of the personality and having to do with a more complete study of unconscious mental forces, only hints of which are contained in this report. Such studies would necessitate the psychoanalytic method., the application of which to the problem of the organ neuroses is a vast subject the surface of which, as yet, has only been scratched.

Whatever one believes regarding the etiological role of these mental forces, it must be apparent that to study patients with cardiospasm simply as physiological mechanisms and treat them by mechanical measures, without making some effort to understand the emotional make-up, is a very one-sided and inadequate attempt to deal with the disorder. The above observations suggest the necessity for a combined physical and psychological study and treatment of the individual patient with cardiospasm. No one can deny the necessity for mechanical treatments in the established case of cardiospasm but is it not possible that this additional psychic approach will help us deal with that group of cases "which tends to recur" or that group "which cannot be cured." Especially in regard to these groups we must consider the frequent observation that in a patient with a severe neurosis a physical disorder (such as cardiospasm) appears to be that patient's solution of his psychic conflict. The physical disorder, therefore, is necessary to the emotional life and until the psychic conflict is better solved, the particular disorder from which the patient suffers either must be maintained or must be replaced by another illness. Certainly, in an early case of cardiospasm, especially in a young person, psychologic study and treatment seem to me an essential part of the management. Indeed, I venture to suggest that the time is approaching when the physician will consider the neglect of psychological study just as serious an omission, in the total study of the patient with cardiospasm, as the failure to X-ray such a patient or study him with the esophagoscope.

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Epigastric Percussion in Peptic Ulcer*

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THE paucity of definite physical signs in patients with uncomplicated peptic ulcer is well known. The tendency to seek laboratory confirmation of the diagnosis of peptic ulcer by the use of the X-ray and test meals has tended in no small measure to an almost complete neglect of a clinical sign which, in the past, has been considered a valuable diagnostic aid.

In 1903 Mendel (1) published an article entitled, *"The Direct Percussion of the Epigastrium,"* calling attention to the localization of pain to the epigastrium by gentle percussion with a reflex hammer in patients with peptic ulcer. Boas (2) in speaking of this sign

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says, "that he elicits a pain response by a reflex hammer percussion much more definitely than by finger percussion or pressure." Boas' sign is a pain elicited by percussion to the left or less commonly to the right of the 10th-12th dorsal vertebrae and is not to be confused with the Mendel test. The chief objection to the Mendel test is that pain may be elicited from various points over the abdomen in a sensitive or hypersensitive patient who has no organic disease. It occurred to one of us that Libman's (3) styloid pressure test could be used to determine the degree of sensitivity in conjunction with the Mendel test. Crohn (4) has suggested a similar procedure in estimating epigastric tenderness to pressure.

For a number of years one of us has been impressed with the clinical importance of the test as described by Mendel and has employed it with the following modification. The Mendel test is first performed by gentle percussion with a reflex hammer (with a triangular rubber head) over the abdomen, employing rapid and short strokes. The epigastrium is gradually approached. In *positive* cases, pain is definitely elicited and localized to a small area either over the mid-epigastrium or 1 to 2 cm. to the right of the mid-line. The patient will react by wincing or by actually pointing to the local area of pain or tenderness. In *negative* cases, the patient will either fail to wince or will point to many areas of pain. Immediately following the percussion of the abdomen the sensitivity of the patient to pain is determined by Libman's styloid pressure method. Libman determined the sensitivity of patients to pain by pressing over the styloid processes. He divides patients into two major groups, sensitive and hyposensitive. He considers patients sensitive (+++ sensitive) if they give evidence of marked pain or admit that the test is definitely painful. Hyposensitive patients either give no evidence of pain and state that they feel none (0 — sensitive) or give evidence of little pain and admit, on questioning, that some pain is felt (+ — sensitive). Using this method as a control of the sensitivity of the individual we have been able to evaluate in a more definite manner the Mendel percussion test. Thus it becomes apparent that a positive pain localization by percussion of the epigastrium in an hyposensitive patient is of diagnostic value in patients with peptic ulcer.

TABLE I

Patients With Ulcer Story

X-ray	Number	Positive Response to Percussion Test	Hyposensitive	Sensitive
Ulcer Defect	48	36	33	3
No Ulcer Defect	14	4	4	0
Total	62			

The X-ray examination, abdominal percussion and *sensitivity to pain (Table I) were studied in sixty-two* patients with a history typical or suggestive of peptic ulcer. Fluroscopic examination revealed an ulcer defect in forty-eight patients, thirty-six of whom exhibited a positive reaction to pain on percussion of a localized area in the mid-epigastrium or slightly to the right of the mid-line. The styloid pressure test demonstrated that thirty-three of the thirty-six patients were hyposensitive.

Of the fourteen patients without a demonstrable ulcer defect, four exhibited a positive pain reaction on epigastric percussion. All of the four were found to be hyposensitive. It is of interest to note that subsequent fluroscopic examination of one of these four patients revealed an ulcer defect which disappeared on ulcer management. Another had several hemorrhages from the upper gastro-intestinal tract *during the following three years though at no time* did X-ray reveal an ulcer.

Forty-three patients without an ulcer history but suffering from various diseases (arthritis, diabetes mellitus, etc.) were studied as to the reaction to abdominal percussion and sensitivity to pain. No X-ray studies were made. A positive pain response on percussion was elicited in six. All but two of the entire groups were hyposensitive. (Table II).

TABLE II

Patients Without Ulcer Story

Number	Positive Response to Percussion Test	Hypersensitive	Sensitive
43	6	42	1

In five patients with cholelithiasis a positive response to percussion was elicited, but the area of tenderness was larger and located over the right upper quadrant. All were hyposensitive according to Libman's test.

SUMMARY

We direct attention to the gentle percussion with a reflex hammer of the epigastrium in patients with peptic ulcer as a diagnostic aid and suggest it be controlled by Libman's test for pain sensitivity.

Our experience indicates this modification of the Mendel test as valuable in the presence of a typical history of peptic ulcer.

With an atypical history, the determination of localized epigastric tenderness by gentle percussion suggests peptic ulcer. This is made more certain if the patient is hyposensitive.

In an hyposensitive patient with a typical ulcer history but in whom an ulcer defect is not demonstrated, the Mendel percussion test is of diagnostic value.

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On the Anemia Following Gastric Operations

By

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A NUMBER of comprehensive clinical investigations (1-16) have indicated that post-operative anemia is a relatively common finding after gastro-enterostomy or gastric resection. A large number of authors have described isolated cases of either pernicious anemia or a "grave anemia" following gastro-enterostomy or extensive gastrict resection (17-22, and numerous others during the past decade) after various intervals of time. These cases now number about two hundred. Further, hypochromic anemia has been produced experimentally by means of total gastrectomy in dogs (23-28, 6), rats (29-31) and pigs (32, 33). However, a hyperchromic post-operative anemia has not been successfully provoked, and it is well known that in man post-operative hyperchromic anemia is comparatively rare, while the hypochromic form is relatively common.

When the anemia appears many years after the operation it is natural to consider it independent of the operation. Of course, it is also necessary to exclude those cases, in so far as is possible, in which pathological processes existing prior to or after the operation may account for the anemia.

It is believed that post-operative anemia is more extensive than is generally recognized, because several factors operate in ordinary clinical practice to hide its incidence. As Gordon-Taylor (3) has pointed out, the patients are often only slightly, or not at all, troubled by the anemia and do not consult a physician, and the anemia is not discovered by the questionnaire method which is so commonly employed for post-operative examination. If exact figures of the incidence of post-operative anemia are to be obtained, the patient's blood must be examined, a procedure which is frequently beset with practical difficulties. Recently, however, a few such studies have been made (2, 3, 7, 8, 9, 12, 13), from which material a frequency of from 25 to 50 per cent has been obtained.

The author cannot present such a frequency figure, because the source of his data is different, but nevertheless instructive. My data comes from a study of those patients which were secondarily treated in the medical department for non-hemorrhagic post-operative complaints. As early as 1931, after a study of such patients in the Seraphim Hospital between the years 1919 and 1928, the author expressed the decided opinion that the occurrence of post-operative anemia following operations on the stomach is relatively common (4). Although the patients most commonly had a hypochromic anemia, several had a hyperchromic anemia with the typical blood picture of pernicious anemia. Since 1928 the author has continued to study similar patients, which were kindly placed at his disposal by the respective heads of the medical departments at the Sabbatsberg Hospital in Stockholm.

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OBSERVATIONS

The results of this latter study are briefly summarized in Tables I and II. It is to be noted that blood studies were made on forty-six patients. Twelve of the twenty-six males had a "mild" anemia and three a "well-marked" anemia. Eight of the female patients had a "mild" anemia and nine had a marked anemia. Or, 69 per cent of the patients suffered from anemia. Seven of the forty-six patients had been subjected to the Billroth II operation, and of these only one had a normal hemoglobin and red cell value. In the remaining thirty-nine gastro-enterostomy patients, the pyloric antrum had been resected in six. All of these had anemia.

TABLE I

Distriution of Patients With Reference to Blood Values

	Normal values	Mild anemia	Well-marked anemia	Number of examined cases
Males	11	12	3	26
Females	3	8	9	20
Sum total	14	20	12	46

TABLE II

Distribution of Patients With Reference to Operation and Blood Values

		Normal values	Mild anemia*	Well-marked anemia	Number of examined cases
Gastro-enterostomy	Males	11	10	2	23
	Females	2	4	4	10
	Total	13	14	6	33
Gastro-enterostomy with exclusio pylori	Males	0	1	1	2
	Females	0	2	2	4
	Total	0	3	3	6
Billroth II	Males	0	1	0	1
	Females	1	2	3	6
	Total	1	3	3	7
	Sum total	14	20	12	46

**Note*: "Mild anemia": In men = haemoglobin 70-80%, red blood corpuscles 4-4,9 mill. or both these values simultaneously; in women = haemoglobin 65-70%, red blood corpuscles 3.7-4.4 mill. or both these values simultaneously. Values falling below those submitted for "mild" anemia are referred to as "well-marked" anemia.

It cannot be concluded from the author's material whether anemia is more common after subtotal gastric resection than after gastro-enterostomy. Evidence bearing on this question has not been found in the literature. However, the data submitted gives the impression that resection is more likely to lead to

anemia than is gastro-enterostomy. It would appear to be quite evident that post-operative anemia is more likely to occur in women than in men.

DISCUSSION

A question of the greatest interest, which must still be considered as only partially solved, is the cause of post-operative anemia. The final solution of this difficult problem is probably also of great importance for the elucidation of the cause of certain other forms of non-post-operative anemia, which have not yet been fully investigated.

A gastric insufficiency following an operation, possibly associated with achylia, achlorhydria or hypochlorhydria as an expression of this injury, will probably prove to be the chief cause of the anemia appearing after the operation. In such cases, the anemia usually takes the form of simple achylic anemia (Faber's anemia), and more exceptionally the form of *anemia perniciosa*. In other cases, again, it must be assumed that the cause of the anemia is to be sought, at least partly, in the reduction of the size of the stomach, so-called "agastric anemia" (Morawitz, *ref.* 34). It is probable that in both these groups the cause is one and the same. Corroborative evidence of this is found not only in the well-known works of Faber (35) and his followers on the connection between achylia, achlorhydria or hypochlorhydria and different forms of anemia, but also in the pioneer investigations published during the last few years by Castle (35, 36) and his collaborators on "the intrinsic and extrinsic factor." From these works we have obtained a knowledge of the fundamental importance of the stomach and its functions as related to the occurrence and prevention of both hypochromic and hyperchromic anemia.

The *antrum pylori* appears to be the part of the stomach which is most active in producing the substance which, in healthy persons, prevents the occurrence of pernicious anemia. Henning and Brugsch (37) have made a comparative test of the antianemic effect of the mucous membrane of the fornix, fundus, antrum and duodenum. These investigators, and later Meulengracht (38), found that the mucous membrane of the antrum was the most active. It would appear that the more extensive the gastric resection, the more likely post-operative anemia will occur, or the more the patient must depend on the "intrinsic factor" in the intestine.

It is more difficult to explain the occurrence of anemia in those patients in which post-operatively the secretion of acid is found to be within the normal range. Such cases have been observed (2, 3, 4, 6) and must be taken into account, even though it must be acknowledged that post-operative anemia and achylia, achlorhydria or hypochlorhydria, usually are found together. In patients showing post-operative anemia with maintained acid production, as well as in many other cases of post-operative anemia, the cause is to be sought in the disturbances of the physiology of the digestive organs, and factors connected therewith, consequent to the operation as well as in the stomach itself. The circumstance that an exclusion of the pylorus, carried out in connection with simple gastro-enterostomy or resection (Billroth II), seems to increase the propensity to post-operative anemia (4, 9) speaks in favor of this. The tendency observed by Morley and Roberts (2) and recently by Fasiani (15) and Chiatellino (16) of the Billroth II operation to give rise to anemia to a greater extent than the Billroth I, also, points in the same direction. Further, it may be indicated in this connection that Dedichen (8) found post-operative achylia to be associated with anemia more often than non-post-operative achylia. This observation indicates that in post-operative gastric cases there must be some factor, other than achylia which predisposes to anemia. It may rationally be assumed that in some cases this factor is identical with the disturbances just referred to in the physiology of the digestive organs consequent to the operation.

How is the apparent relation between the disturbances in the physiology of the digestive organs and the anemia to be conceived? Exclusion of the pylorus, regardless of whether it is made in association with gastro-enterostomy or resection (Billroth II), prevents nourishment from following the physiological path from the stomach through the duodenum. In gastro-enterostomy, unaccompanied by exclusion of the pylorus, the passage of nourishment is more complicated, but in general the nourishment follows the direct path from the stomach into the jejunum. In the event that nourishment does not pass through the duodenum, the normal stimulation of this section of the intestine, which affects the secretion of the liver and pancreas, is absent. The result is that in such patients, the secretion of the liver and pancreas depends on the weaker and less specific stimulation from the jejunum and the ileum. In other words, the liver and pancreas are partially disconnected from the digestive system. In this connection it is of interest to point out that Strandell (39), in experiments with the injection of the liver preparation, "Heptomin," has observed a very pronounced reticulocyte response and a rapid change for the better in two grave cases of hypochromic anemia following gastro-enterostomy, one of which, with *exclusio pylori*, reacted in the same way as a case of anemia perniciosa. In neither Lublin's nor Dedichen's data could any correlation be shown between the frequency of post-operative intestinal disturbances and post-operative anemia, a circumstance which to some extent affords corroborative evidence that the cause of anemia is probably to be sought rather in the stomach, duodenum, liver, and perhaps pancreas, than in the lower intestine.

It should be of the greatest interest from the viewpoint of the cause of post-operative anemia to investigate the effect of *inter alia exclusio pylori* on animals, such as the pig, and to obtain post-operative blood examinations on patients who have undergone this operation.

SUMMARY

Blood studies have been made on forty-six patients who returned to the medical clinic for various complaints, other than hemorrhage, following either a gastro-enterostomy with and without exclusio pylori or Billroth II operation. Sixty-nine per cent of these patients had a hypochromic anemia. Six of the seven patients subjected to the Billroth II had varying grades of anemia. In six of the gastro-enterostomized the pylorus had been excluded; all had anemia. Post-operative anemia was more frequent in the females than the males. Observations bearing on the cause of anemia following operations on the stomach are discussed.

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Incidence of Malignancy in Gastric Ulcer*

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THE academic question of transformation of gastric ulcer into cancer has been a much disputed one. The figures quoted varied widely and as yet no definite agreement seems to have been reached. As summarized in the reviews of this subject by Cabot and Adie (1) and by Hurst and Stewart (2) malignant degeneration of gastric ulcer probably does not take place very frequently, certainly not much exceeding 5 per cent. In actual practice, the more pertinent question to the physician is, however, not how many of his gastric ulcer patients will later develop malignant disease of the stomach but rather how many already have it.

That a malignant gastric ulcer may present most or all the features of a benign one is undoubted by experienced observers. Not infrequently a carcinomatous ulcer may occur in a young individual, may be associated with a relatively long history and a normal or high gastric acidity, and on X-ray examination may reveal a comparatively small ulcer crater. In fact even the surgeon having the ulcer in hand may at times have difficulty in deciding the issue. It, therefore, behooves us to inquire into the incidence of carcinoma among cases of clinical gastric ulcer. This information is specially desirable in the immediate management of such patients as it has a direct bearing on the form of treatment to be followed.

The present communication deals with an analysis of 63 cases of gastric ulcer treated in Lane Hospital, with a view to clarifying the point in question.

Description of Cases. In the cases presented below the diagnosis of gastric ulcer was ascertained both clinically and roentgenologically. Special care was taken in reviewing the roentgen films and fluoroscopic record of each case, any one with the slightest suspicion of frank neoplasm being excluded. The writer is indebted to Dr. R. R. Newell for permission to use the roentgenological data. Lastly, only those cases in which the record fulfilled one of the required criteria are included in this study.

TABLE I

Age Distribution

Age in years	Number of cases
11-20	1
21-30	5
31-40	11
41-50	15
51-60	17
61-70	10
71-80	2
81-90	1
Unknown	1
Total	63

Forty-eight of the 63 cases occurred in the male and 13 in the female. The age varied between 13 and 82 years, the majority of the patients being in the 3rd, 4th, and 5th decades (Table I). The duration of symptoms is shown in Table II. When the patients first came under observation the gastric complaints

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had been present for one year or less in 40 per cent of the cases, and for more than five years in 33 per cent. The site of the ulcer was the pylorus in 15 cases, lesser curvature in 44 cases, and cardia in 2

TABLE II

Duration of Symptoms

Duration	Number of Cases	Percentage
1 month to 6 months	19	30.2
7 months to 12 months	6	9.5
1 to 2 years	7	11.1
2 to 3 years	3	4.8
3 to 4 years	2	3.2
4 to 5 years	4	6.3
More than 5 years	21	33.3
Unknown	1	1.6
Total	63	100.0

cases. The size of the ulcer is shown in Table III. In 20 cases the ulcer was described as of the penetrating type. Nearly half of the patients (30 cases) had six-hour retention, mostly (14 cases) amounting to less than 50 per cent of the barium meal. As regards the gastric acidity, there were 3 instances of achlorhydria, one confirmed by histamine test. Four patients had hypoacidity (highest titratable acidity of 20 c.c. 0.1

TABLE III

Size of the Ulcer

Diameter	Number of cases
Less than 1 cm.	4
1 cm.	14
2 cm.	11
3 cm.	6
4 cm.	4
"Small"	6
"Large"	5
Not noted	13
Total	63

N per 100 c.c. or less after Ewald meal, or of 40 c.c. 0.1 N per 100 c.c. or less after alcohol meal or histamine injection) and 21 patients had hyperacidity (highest titratable acidity of 40 c.c. 0.1 N per 100 c.c. or more after Ewald meal, or of 100 c.c. 0.1 N per 100 c.c. or more after alcohol meal or histamine injection). In the remaining instances (26 cases) in which gastric analysis was done the acidity was normal.

Diagnostic Criteria. As has been said above, the exclusion of malignancy in cases of gastric ulcer is an extremely difficult matter. The most accurate method of diagnosis remains microscopic examination of the lesion, as by no other means can one say with certainty that an ulcer in question is of benign or malignant nature. In 16 cases of the present series this examination was made either after operation or on autopsy. Next to microscopy, careful inspection of the gross lesion seems to be a fairly reliable though not infallible means of differentiation. On the operating table the surgeon can ascertain at least the size, location, and consistency of an ulcer much more accurately than the internist or roentgenologist. It is true that surgeons do encounter difficulties at times and a diagnosis of benign ulcer based on operative data alone must rest open to some doubt. On the other hand when visible metastasis is already present it practically settles the issue in favor of malignancy. There were only four patients in this series in whom the diagnosis had to be decided by operation, two being benign and two malignant. Besides these two criteria, we have, in the remaining instances (62 cases), relied on the course of the disease for probable diagnosis. We assume that any patient who, after first coming for treatment, had lived for two years or longer with no clinical evidence of malignant disease, probably did not suffer from gastric carcinoma at the outset. This is necessarily arbitrary and certainly does not rule out malignant change of the ulcer in the future. Nevertheless it seems to be a relatively safe working basis, especially if it is borne in mind that at the time of their first visit 60 per cent of the patients had already suffered from gastric symptoms for more than one year.

In summary, our criteria of differentiation between benign and malignant gastric ulcers consist of: (1) Histological examination, (2) Operative data, and (3) Clinical course of the disease.

Of the 63 cases, two were those of gastric carcinoma, both proven by operation and clinical course combined. A third case of lymphosarcoma was diagnosed by histological examination of the ulcer after surgical removal. In a fourth case the clinical picture was very suggestive of carcinoma but the positive blood Wassermann reaction, the subsequent course, and the speedy response to anti-syphilitic treatment made the diagnosis of gastric syphilis highly probable. The details of these cases are abstracted in the case reports. The remaining 59 cases are classified as the benign ulcer in accordance with one or more of the criteria described above (Table IV). In only two cases was the diagnosis of benignancy somewhat in doubt as it was based on operative data alone. In the 46 cases in which benign ulcer was diagnosed by the clinical course, either alone or with one or more other criterion, 14 patients were followed for 2 years, 6 for 3 years, 10 for 4 years, 14 for 5 years or more and 2 for 10 years or more.

TABLE IV

How the 59 Cases of Benign Ulcer Were Diagnosed

Criteria	Number of cases
Clinical course alone	32
Microscopic examination alone	11
Microscopic examination and clinical course	1
Operation alone	2
Operation and clinical course	10
Total	59

To recapitulate, in the 63 cases of roentgenologically and clinically diagnosed gastric ulcer, malignancy was definitely present in 3 instances (2 carcinomatous and 1 lymphosarcomatous). Including a fourth questionable case in which gastric syphilis could not be ruled out, the incidence of malignancy was approximately 6.4 per cent.

DISCUSSION AND SUMMARY

The purpose of this study, in brief, was to obtain further information as to how often apparently benign

gastric ulcers are really malignant. It was assumed that if the patient showed no signs of cancer after a two year observation period the original diagnosis of simple peptic ulcer was correct. On this basis it turned out that three of 63 instances of apparently benign ulcer were really malignant or soon became so. This corresponds with current opinion that probably not more than five per cent of peptic ulcers show malignant change.

CASE REPORTS

Case 34. Lymphosarcoma—An American housewife of 45 complained of cramp-like pain in the right lower quadrant for five months. The pain radiated to the back and left costal margin. It was not related to food. Nausea and vomiting accompanied the pain. The gastric acidity was normal. X-ray revealed a large perforating ulcer on the lesser curvature of pars media of the stomach. Pylorectomy and posterior gastroenterostomy were performed. Histological examination showed a chronic ulcer with lymphosarcomatous base. No metastasis was found. The patient was living and well five years after the operation.

Comment. This case represents the ulcerative type of lymphosarcoma. The tumor was probably primary in the stomach and was not associated with generalized lymphosarcomatosis. The absence of demonstrable metastasis and surgical removal of the ulcer most likely accounted for the patient's survival at the end of five-year period.

Case 38. Carcinoma—A married woman of 52, with ulcer syndrome for 16 years, had an ulcer, measuring 1.5 cm. in diameter, on the lesser curvature, 4 cm. proximal to the pylorus. There was high gastric acidity and 30 per cent retention at the end of six hours. Having failed to improve on medical treatment the patient was operated on in August, 1931, and posterior gastroenterostomy was performed for an apparently benign ulcer. The patient had only slight symptomatic improvement. Roentgenological examination one year after the operation showed an irregular pyloric antrum and a mass in the epigastrium and exploration in January, 1934, revealed an inoperable carcinoma of the stomach.

Comment. In this case the carcinoma undoubtedly had existed in 1931, at the time of her first operation. This was suggested by the slight or absent improvement following gastro-enterostomy. It is difficult to evaluate the long history. Possibly carcinoma had developed on a previously benign ulcer. When the patient first came under observation, the picture was essentially that of gastric ulcer and no suspicion of malignancy was aroused even by the surgeon who operated on the patient the first time.

Case 53. Carcinoma—An American laborer of 53 had epigastric pain from two to three hours after meal for four years. The pain was relieved by food, soda, and vomiting. The symptoms had increased in severity for one month. The gastric acidity was normal. On X-ray examination, an irregular ulcer, 2 cm. in diameter and 1 cm. in depth, was demonstrated on the lesser curvature just above the *incisura angularis*. A greater curvature deformity was present opposite the ulcer. The ulcer was resected. Histological examination of the ulcer and regional lymph node showed no evidence of malignancy. There was, however, suspicion of metastasis in the liver and seven months after the operation a large mass was found in the epigastrium, "undoubtedly carcinomatous recurrence."

Comment. This patient most likely suffered from gastric carcinoma. It is hard to explain the negative biopsy findings but the presence of metastasis in the liver and the subsequent development made this diagnosis practically certain.

Case 64. A 43-year old American salesman had upper abdominal pain two hours after meal for ten years. No free hydrochloric acid was present in the gastric juice after injection of histamine. A large ulcer, measuring about 4 cm. in diameter, was located by X-ray examination, on the lesser curvature, 4 cm. above the *incisura angularis*. Six-hour retention amounted to 30 per cent. The blood Wassermann reaction was strongly positive. Treatment with diet and potassium iodide was instituted and on subsequent roentgenological examinations the gastric lesion showed steady improvement, no ulcer creater being discoverable ten weeks afterwards. The patient, when seen one and one-half years later, remained symptomless.

Comment. In this case the achlorhydria and the size of the ulcer pointed to malignancy. The fact that treatment with potassium iodide brought about rapid improvement would instead speak in favor of gastric syphilis. The patient's good health and freedom from gastrointestinal symptoms for many months would also seem to argue against carcinoma.

The writer wishes to express his indebtedness to Dr. A. L. Bloomfield for advice and encouragement and for permission to study the clinical records of the cases reported in this paper.

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The Double Histamine Test as an Aid in the Study of Gastric Secretory Function*

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AFTER the subcutaneous administration of histamine hydrochloride or histamine acid phosphate there is usually a marked increase in the secretion of the digestive juices. The recognition of this physiologic action resulted in the use of histamine as a diagnostic agent in the study of the secretory potentiality of the gastric glands.

The efficacy of histamine in provoking increased secretion of gastric juice is unquestioned. A point of

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controversy remains, however, since it is still debated whether or not the enzyme fraction of gastric secretion is increased after the use of this drug. Some observers (Babkin, Gilman, and Cowgill), though noting the increase in the peptic activity of gastric juice following the use of histamine, assume that this is due to a washing out of the peptic glands accompanying activation of the secretion of large amounts of hydrochloric acid and other inorganic constituents of the gastric chyme. Polland, as well as Blakely and Wilkinson, on the other hand, report observations which suggest that the administration of histamine results in an increased output of pepsin. Blakely and Wilkinson furthermore stated that a second dose of histamine had on the whole a slightly less effect, although in one case only the second dose effected the increase. The concentration was either increased or decreased, more often the former. That the test has unquestioned value in differentiating an apparent from a true achylia gastrica seems now to be an established fact. It should not be assumed, however, that this is invariably true, because there are a few instances in which an Ewald test meal provokes secretion of free hydrochloric acid even when such secretion does not occur following the use of histamine.

For some time we at this Clinic have been interested in applying some principles of gastric function, which can be measured by the histamine tests, to certain of the problems incident to the etiology, chronicity and therapeusis of peptic ulceration. The only common denominator which is consistently and readily applicable to peptic lesions is that they occur in tissues bathed by the acid gastric chyme. Ultimately, the various interrelated factors important in the causation of ulcer would seem to resolve themselves mainly into two main factors: the one inherent in the ulcerating potentiality of acid pepsin, the other maintained in the defenses which the tissues possess and by which they protect themselves against the eroding action of gastric chyme.

Physiologists have amply demonstrated the increased vulnerability of tissues to gastric juice of high acid pepsin value. It has often been noted that, following the use of histamine, patients with peptic ulcer continued to secrete a highly concentrated acid *for considerable periods after a retardation of secretory rates would ordinarily have been expected.* If such cellular behavior actually obtains in response to other stimuli, it would be obvious that the gastroduodenal defense mechanisms of patients with peptic ulcer might be forced to exert themselves accordingly. It seems logical that the activity of the defense mechanisms would have to fluctuate in proportion to changes in the potency of the acid-pepsin mechanisms of aggression; with prolonged and sustained elevation of acid pepsin secretion there would develop the requirements for a correspondingly vigorous effort on the part of the cells to throw out defenses against such accentuated tendencies to erosion. Ordinarily, Nature has provided that there be alternate periods of rapidity and retardation of the gastric secretory rate, thus giving the gastroduodenal cells "breathing spells" during which the forces of defense could be adequately reëstablished. Though the duodenum has remarkable reserve function in neutralizing and buffering acids, which is naturally in excess of its ordinary physiologic requirements, it will break down, however, as shown by the work of many physiologists, under the continued necessity of neutralizing the acid chyme.

Hence, the height of acid concentration and of peptic activity may be overshadowed in importance by the tendency of the chief and parietal cells to *maintain* vigorous secretory rates for unusually long periods of time. Since this maintenance of attenuated and prolonged secretory rates may represent a specific "ulcer-producing" tendency in certain patients, effort should be made to measure the potency and persistency of this factor. We at this Clinic therefore began to analyze the acid fractions as well as the peptic activity following the use of histamine for longer periods than previously. Thus we were able to measure not only the height of acidity, but also the length of time following the use of the stimulating substance through which the chief and parietal cells maintained increased secretory rates.

It then occurred to us that since it was important to know not only the maximum secretory potential of the cell, but also to have information regarding the tendency of these cells to continue to secrete with increased vigor, more might be learned by applying a second stimulation by means of histamine to the gastric glands after the estimation of the fractions gave evidence that secretory rates had approximated those present before the histamine was given. In some instances the persistence of increased secretory rates was so protracted that the second injection of histamine was made before there was much drop in acidity. Thus it was possible to observe the secretory response of the chief and parietal cells over a period of two, or sometimes three, hours. In this way it was believed that more accurate measurement of the behavior of these cells might become available.

The object of this paper is mainly to call attention to the possible usefulness of this test in adding to knowledge of gastric secretory rates. In a subsequent paper it is our intention to analyze more fully the results obtained in cases of peptic ulcer. Included in this paper, however, will be certain observations regarding acid responses in general, as well as some observations regarding the activity of peptic secretions, as noted following the use of the double histamine test.

In performing double histamine tests a small-bore Sawyer tube was introduced into the stomach and the contents were aspirated as completely as possible, after which the contents were evacuated at ten-minute periods, and in certain instances fifteen-minute periods,

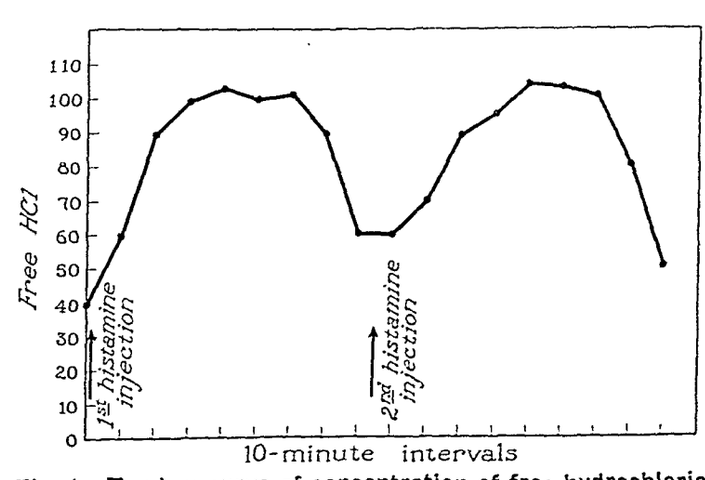


Fig. 1. Tandem curve of concentration of free hydrochloric acid produced by two injections of histamine.

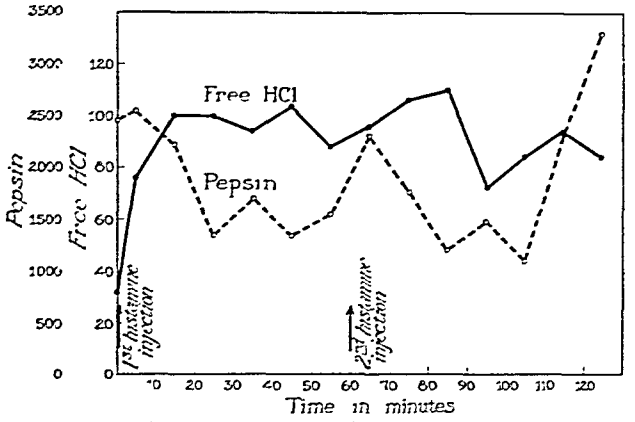


Fig. 2. Continuous black line indicates concentration of free hydrochloric acid; broken line, peptic activity following two injections of histamine.

during which unstimulated fasting secretion was removed. Histamine was then injected subcutaneously in doses of 0.1 mg. for each 10 kg. of body weight. Following this, gastric juice was aspirated for six periods of ten or fifteen minutes each. Then the same amount of histamine was again injected subcutaneously, and specimens were collected for six more periods of ten or fifteen minutes each. The volume of each specimen was measured and the concentration of acid of each was determined by titration with tenth normal sodium hydroxide, using Töpfer's reagent to determine free acid and phenolphthalein for total acid. Concentration of pepsin was estimated by the modification of the Gilman-Cowgill method described by Osterberg. Figures representing quantities of acid and pepsin secreted for each period of ten or fifteen minutes were obtained by multiplying the concentration of the substances in each specimen by the volume of the specimen.

Figure 1 shows a double or tandem curve indicating the concentration of free hydrochloric acid following two injections of histamine. The curves are fairly representative of the usual effect on gastric acid secretory mechanisms when a second injection of histamine is given sixty to ninety minutes after the first. This second response of the parietal, and incidently of the chief cells as well, is usually similar to the first.

Occasionally, in some cases there is a marked difference in the two curves, and in such instances the test may be of no particular value. Usually, however, not only is the maximal concentration of acid similar, but the persistence of cell activity indicated by the width of the curve is the same. If it has been established that in the original double histamine test both curves were similar, subsequent examinations performed within a period of two or three weeks usually again exhibit similar characteristics in both curves. Hence the second or trailer curve of subsequently performed tests can be plotted as an "expectancy" curve. Frequently, it is important to know the effect of certain ingested or injected material on the gastric secretory function. Such substances can then be given before the second injection of histamine is made. If the resultant second curve now shows gross deviation from the expectancy curve, evidence is available to suggest that the tested material was responsible for such changes in gastric chemism.

The response of the peptic cells is usually very similar to that observed in the behavior of acid cells following the use of histamine. There are many instances in which peptic activity during the course of the second histamine test was higher than it was during the course of the first test. This suggests that pepsin is not washed out from the gastric glands, but rather that it is a direct result of the stimulatory effect of histamine on the chief cells. It can be noted from a study of the pepsin curve in Figure 2 that peptic activity reached its maximum one hundred twenty minutes after the first histamine injection. It is also evident from a review of this figure that there was no retardation of acid secretory rates sixty minutes after the first injection of histamine. In such instances readings should be made at fifteen rather than at ten minute intervals and the second histamine injection should be made ninety minutes after the first. This type of curve is frequently seen in patients having a tendency toward the formation of peptic ulcer.

The secretory response of gastric cells following the use of histamine as an excitant exhibits marked inconstancy under varying circumstances. Though the behavior of the chief and parietal cells following the use of histamine may be measurable with accuracy, this probably represents only the potential response of these cells at the particular time when the test is made.

In Figure 3 are represented the curves of acidity following the use of histamine under varying conditions. In this case the vigorous secretory rate (curve A) occurs during periods in which the symptoms of ulcer are present. During periods of quiescence the rate of secretion was markedly retarded, and its response was that usually seen in normal individuals (curve B). It must not be assumed, therefore, that a single test represents a constant from which there will be no deviation in subsequent examinations. To draw conclusions based on the changes evident in curves of acidity following single histamine tests, when these tests are made at different times, may result in fallacious deductions.

CONCLUSIONS

First, it is suggested that the double histamine test might be useful in obtaining information, not only regarding the maximal potentiality of acid and pepsin secretion of gastric cells, but also regarding the

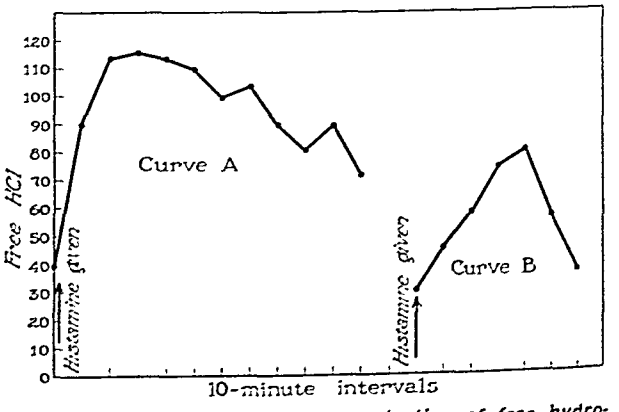


Fig. 3. Curve A represents concentration of free hydrochloric acid following administration of histamine during period of activity of ulcer. Curve B represents concentration of free hydrochloric acid following administration of histamine in period of quiescence of ulcer. Both curves represent data from same patient.

maintenance of increased secretory rates over longer periods of time. Unquestionably, this information is important. Second, by means of this test it seems possible to test with greater accuracy the effect of test substances on gastric chemistry. Third, a review of the results obtained in the double histamine test suggested the probability that the subcutaneous injection of histamine results not only in a washing out of the peptic glands, but actually in a stimulation of the chief cells to increased activity.

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Phytobezoar with Visualization by Means of Gastroscopy

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BEZOARS have always caused considerable interest. In ancient times they were highly prized as charms, and valued as curative agents for various diseases. Matas, in 1914, presented an excellent antiquarian review of the disease and its history. With increase in knowledge the interest shifted to a study of the method of formation, antemortem diagnosis, and proper treatment. In spite of the excellent articles that have appeared on the subject, the number of reported cases has remained relatively limited. The case we wish to report is that of a phytobezoar, and is of special interest not only on account of the surgical treatment, but also because it is the first time that such a tumor has been visualized and recognized preoperatively by direct visual means.

Bezoars may be divided into many types, dependent on their composition. The great majority fall into one of four groups: trichobezoars or hair balls: phytobezoars, or food balls; trichophytobezoars, which are a combination of the first two; and concretions. The relative infrequency of the tumors is indicated by the report of Maes, in 1928. He was able to collect only 139 cases of bezoar from the literature, and phytobezoar had been present in only twenty-three of these cases. Smith, in 1933, brought the number up to fifty, exclusive of an indeterminate number of Harparaballi bezoars reported from India. Undoubtedly, many more, which have not been reported, have been encountered in practice, while others, which have terminated fatally, remained unrecognized, or were thought to be malignant, as in a case reported by Adams.

The etiology of phytobezoars has not been adequately determined. Balfour and Good expressed the opinion that the etiology is not dependent on any one factor. There is reason to believe, however, that they are formed at one time, as layers of accretion are not found on section. Hart and others have called attention to the high percentage of cases in which persimmons act as the primary base of phytobezoars, and said that this fruit contains a high percentage of gum and pectin, which may act as a cohesive element. This factor does not, however, hold good for other types of food, such as prunes, salsify, celery, pumpkin, and other substances, which may give rise to the formation of phytobezoars. One of the most striking features of the history of the disease is that the patient invariably has overindulged in the substance which comprises the tumor.



Fig. 1. Roentgenographic appearance of tumor of the stomach.

The symptoms of phytobezoars, especially in cases in which persimmons have been the cause of the condition, have been admirably described by Hart, and by

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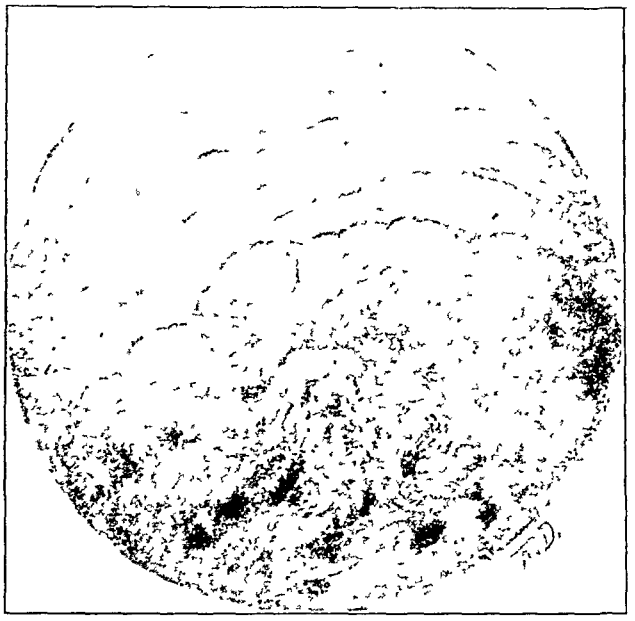


Fig. 2. Gastroscopic appearance of phytobezoar.

Balfour and Good. The symptoms consist primarily of acute gastro-intestinal symptoms, which appear within a few hours or days after the overindulgence in the fruit, if an attack is to occur. Nausea, vomiting, pain and diarrhea are present in varying degree. Smith has emphasized the frequency of hematemesis. After the first acute symptoms have subsided, the findings become bizarre, and are dependent on the size of the tumor. On physical examination, while the patient is properly relaxed, one can frequently palpate a tumor in the epigastrium; the tumor generally is movable, and may be readily mistaken for a malignant tumor. Unless the tumor fills practically the entire stomach and interferes with the ingestion of food, the patient's general health will appear surprisingly good, in the presence of such a large palpable gastric mass. This should focus attention on the correct diagnosis.

The diagnosis of phytobezoar, however, rests primarily on the roentgenoscopic findings. These have already been so excellently described by Camp, Kerr and Rypins, and by others, that they will not be mentioned here.

The treatment is primarily surgical, and this should be the procedure of choice. While relief has been obtained by manipulation and by the administration of dilute hydrochloric acid, these procedures would seem inadvisable. Potter, Butterworth, and others have called attention to the frequent association of gastric ulcer with the tumor. Judd and Phillips and Balfour and Good feel that such complications as ulcers and gastritis are attributable to trauma which is associated with the presence of the foreign body, and that the gastric lesions will rapidly subside after the foreign body has been removed. Such complications in themselves would seem to exclude any violent manipulative procedure.

REPORT OF CASE

A man, aged forty-nine years, came to the Mayo Clinic in August, 1935, complaining of "stomach trouble." He had always enjoyed the best of health until October, 1934. At this time he had gone on a persimmon "spree"; the same night he had been awakened with severe cramping pains in the epigastrium; there had been associated nausea, but no vomiting. The pain had extended across the upper part of the abdomen but had not extended through to the back. The attack had lasted about fifteen minutes, and had passed away spontaneously. Following the attack, he had had somewhat similar daily episodes of epigastric distress which had appeared about 11 a. m and 3 p. m. He always had obtained relief by taking food or milk, but not by taking alkalis. He had followed various forms of therapy without success. In January, 1935, the condition had been recognized as a phytobezoar by roentgenoscopic examination. The patient had been operated on, but, to the surprise of all concerned, no evidence of the bezoar had been found. A small healed ulcer, however, had been noted on the lesser curvature of the stomach. The patient had remained free of symptoms for six weeks following the operation, at which time the former symptoms had recurred, but had not been as severe as they had been before the operation. Roentgenoscopic examination at this time had revealed the same defect which had been noted before the operation, and a diagnosis of phytobezoar again had been made. At the time of the patient's admission to this Clinic, his symptoms were unchanged. On physical examination, a sense of fullness could be made out in the epigastrium, although no definite tumor could be felt. Roentgenoscopic examination of the stomach revealed a large multilobulated tumor in the stomach and several associated smaller masses. It was difficult to displace the large tumor from the cardiac end of the stomach The lesion was thought to be a phytobezoar (Fig. 1). The gastric analysis revealed 150 c.c. of gastric juice at the end of an hour. The value for the total acidity was 56, and that for the free hydrochloric acid was 42, according to the method of Topfer.

From the history and roentgenoscopic findings, a diagnosis of phytobezoar was made, and operation was advised. In view of the previous findings at exploration, the patient requested further corroborative evidence before submitting to operation. Gastroscopy was suggested, and requested by the patient. On gastroscopic examination, a large tumor was found to be situated in the middle and cardiac end of the stomach, on the posterior wall. It was

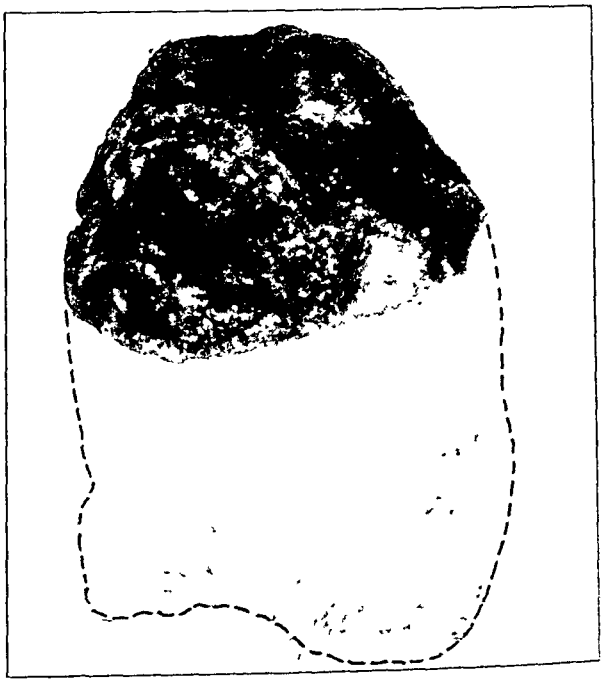


Fig. 3. Phytobezoar after removal; dotted line indicates full size of tumor; exposed portion corresponds to portion visualized with the gastroscope.

impossible to move the growth by pressure with the end of the gastroscope. Figure 2 represents the gastroscopic appearance of the tumor.

With the added information the patient not only was willing, but desired, to undergo another operation. A gastrotomy was performed by one of us (Walters), through a left rectus incision. A movable rock-like tumor mass, approximately 7.5 by 10 cm., was palpated in the lower third of the stomach. A small longitudinal incision was made through the anterior wall of the stomach. Impacted in the lower third of the stomach, just above the pyloric sphincter, was a black ovoid foreign body. It required some force to dislodge this foreign body (Fig. 3). There was a good deal of inflammation in the gastric wall adjacent to and above the foreign body. Exploration of the interior of the stomach with the hand brought out three or four gelatinous-like masses, each about 2 by 3 cm. in size. There was no evidence of an associated gastric ulcer at this time. The incision in the anterior gastric wall was closed in the usual manner. The patient made a rapid and uneventful convalescence, and has remained free of symptoms since the operation.

COMMENT

This case illustrates two salient features: First, bezoars may be movable and at times may escape from the operative field and escape detection, as has been previously described by Outten, in Hart's report. Second, in certain selected cases, gastroscopy may be of value as an added diagnostic procedure.

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Functional Abdominal Distention Simulating Megacolon

By

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FROM time to time, patients present themselves for examination with very marked abdominal distention which simulates organic intestinal obstruction or the distention of megacolon. The diagnosis of intestinal obstruction is usually readily made, but in these cases, careful objective investigation is necessary to distinguish between the distention of intestinal obstruction, true megacolon, and functional abdominal bloating.

REPORT OF CASE

A single woman, aged forty-two years, came to the Mayo Clinic March 18, 1935, complaining of abdominal pain and huge bloating of the abdomen. She had been constipated all of her life and had taken all kinds of cathartics as long as she could remember. She did not remember ever having had a normal bowel movement. However, in the last three years, she had become much worse than she had been; even 4 to 6 ounces (112 to 180 c.c.) of castor oil had not effected a bowel movement. She remembered that as a child she had had a bowel movement every three to five days; at these times, the stools had been as hard as a rock, and she had screamed with pain during the forced passage. During the last thirty years, she always had taken laxatives. In 1918, all of her family, which consisted of six sisters and one brother had had influenza. Besides teaching school, she had nursed these members of her family. During this time, she had had a spell of unconsciousness which had been followed by shaking of the hands which had been diagnosed as "chorea." In 1922, an appendectomy had been performed for recurring pain in the right lower quadrant of the abdomen. Temporary relief had followed. After this, she had had another attack of athetoid movements of the arms and legs, with peculiar facial grimaces, which had lasted for six months. In June, 1931, she had had similar trouble which had lasted for eight months. After this attack, "she had to learn to walk all over again." In October, 1932, she had begun to have what she called a "stomach ache." She first had noticed abdominal distention in December, 1932. Examinations at home had not revealed any organic disorder, and a Mediterranean cruise had been advised. She had become very ill on the boat. The illness had been associated with great distention of the abdomen and much vomiting. She had spent two months in the American Hospital in Paris, where a diagnosis of chronic disseminated encephalomyelitis with super-added psychoneurosis had been made. At that time, the abdominal disturbance had been interpreted as "paralytic ileus." She had returned to America in September, 1933. In June, 1934, she had been on the neurologic service of a large hospital in New York. The abdominal distention had persisted from its

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Fig. 1. Elongation and slight distention of the colon.

first inception in 1932. In July, 1934, her family physician had administered pituitrin, which had produced relief of the abdominal distention, explosive expulsion of gas, and then normal bowel movements. From then until her visit to this Clinic in March, 1935, she had taken pituitrin every one to three days. This had relieved the distention temporarily. She had been sent to this Clinic with the suggestion that she might have a megacolon of the Hirschsprung type.

Examination revealed that the patient was 55 inches (139.7 cm.) in height and weighed 81½ pounds (36.8 kg.). She said that other members of her family were small. The values for the systolic and diastolic blood pressure were 140 and 100 mm. of mercury respectively. This varied from time to time; the average values were 114 for the systolic, and 78 for the diastolic pressure. She appeared to be of a cheerful disposition but obviously was in considerable discomfort. The size of the abdominal distention suggested a full-term pregnancy. The abdomen was soft but somewhat tympanitic. A spinal lordosis was apparent. The digital examination of the rectum at once denied the presence of a megacolon, at least in the distal portion. Proctoscopic examination showed a normal rectal and sigmoid lining. The anal sphincters were large and appeared to be thicker than they normally should be, and two or three times as wide. The lumen of the rectum and sigmoid seemed normal in its dimensions. Roentgenologic studies of the colon showed it to be elongated slightly, and perhaps a little distended (Fig. 1). Fluoroscopic examination of the thorax and diaphragm showed normal diaphragmatic movements. Roentgenograms of the head and of the small intestine did not reveal anything unusual. Repeated urinalyses disclosed that the urine was essentially normal. Examination of the blood did not disclose any abnormality. The value for the urea was 18 mg., and that for the sugar was 94 mg. per 100 c.c. of blood. The values for the sulphates and calcium were 3.5 and 10.1 mg. respectively, per 100 c.c. of serum. The sedimentation rate of the erythrocytes did not reveal any unusual changes.

Further intensive study of the nature of the abdominal distention was undertaken. A bilateral splanchnic block was induced. The patient was placed on the operating table; at this time, the abdomen was moderately distended (Fig. 2a). No peristalsis was audible. There was a marked lordosis of the back (Fig. 2b) and a large hand easily could be slipped between the arched lumbar region and the table. Before five minutes had elapsed following the injection of the procaine in the splanchnic region, the abdominal distention began to disappear. During the most marked flattening of the abdomen, the lumbar region of the back was flat on the table. When the distention began to disappear, peristalsis was audible. This seemed to be of a normal type. There was no passage of flatus or belching of gas during the disappearance of the distention. Among the symptoms noted during the period of splanchnic block were complete aphonia and inability of the patient to sit up on the table. She insisted that she could not see. During this time, the blood pressure, pulse, and the color of the skin were normal. Within fifteen minutes after the injection, the abdominal distention began to recur. Twenty-five cubic centimeters of 1 per cent solution of procaine-novocaine, with epinephrine had been injected. It was one and a half hours before the abdominal distention returned to about its original condition. Sterile normal saline solution, which was injected a few days later in a similar way, produced relief which was less marked than that which occurred after the bilateral splanchnic block. Three days later, the patient again was taken into the operating room. Her knees were flexed and brought toward the head. This caused complete relief of the abdominal distention. At none of these times was gas passed from any of the orifices. Many drugs were administered

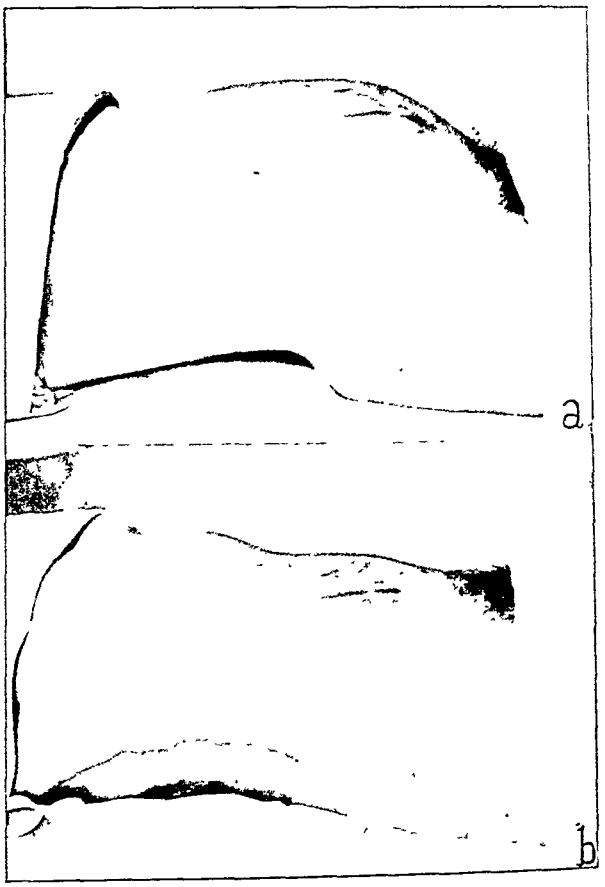


Fig. 2. Condition of abdomen; A, before, and B, after induction of splanchnic anesthesia; injection of physiologic saline solution, injection of sodium ethyl 1-methyl butyl thiobarbituric acid (thionembutal), and other manipulations which distracted the patient's attention.

in an effort to relieve the abdominal distention. Sufficient epinephrine to produce physiologic effect was administered hypodermically, with the thought that this phenomenon might be of the nature of an angioneurotic edema. Physostigmine salicylate was administered in doses which were large enough to produce systemic effects. Tincture of belladonna and sedatives also were administered. None of these drugs gave relief from the abdominal distention. Complete and prompt relief resulted from the injection of surgical pituitrin, and sodium ethyl l-methyl butyl thiobarbituric acid (thionembutal) which was administered intravenously to produce anesthesia, gave prompt relief without the passage of gas. A careful examination of the central nervous system did not reveal any objective organic disease. These tests led us to conclude that the abdominal distention probably had a functional basis. Surgical interference did not seem wise. An anticonstipation regimen and mild sedatives were advised, and she was dismissed on April 22, 1935.

This patient returned to her home. Improvement was only slight and progress did not seem satisfactory. A letter from her family physician, dated September 24, 1935, revealed that a bilateral sympathectomy had been performed and that definite immediate improvement had followed this operation. The letter was dated three weeks after the operation.

COMMENT

Our past experience with cases of this type would lead us to suggest that such a patient should be observed for several years before arriving at a conclusion about the efficacy of any therapeutic endeavor.

Patients with functional abdominal distention present grave problems. There is something about them which smacks of willful invalidism, as in other factitial disorders, and yet if such is the case there seems to come a time when the condition passes beyond the control of the individual. The danger in these cases is the confusion with real organic intestinal obstruction, and hence, of unwarranted surgical interference. A psychologic approach to the problem and a conviction of the functional nature of the condition seems so far to be the keynote to the best treatment.

Pyogenic Skin Lesions Accompanying Chronic Ulcerative Colitis;*

Report of Five Cases

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RECENTLY we have seen five patients who, in the course of ulcerative colitis, developed ulcerations of the skin. This complication, though uncommon, is not only interesting but also important, in that it is often difficult to control. In fact, in one of these cases it was directly responsible for death.

Although a great deal has been written about ulcerative colitis and its more common complications, very little mention has been made concerning skin ulcerations. A rather extensive search revealed but nine such reports. Bargen (1, 2) discussed the condition among other complications. Rankin, Bargen and Buie (3) in their book included a picture of a leg with such lesions.

Warner (4) reported a case of ulcerative colitis in a child, seven years old, with recurring crops of blebs on the skin and mucous membrane of the nose, throat and mouth. The blebs resembled those of pemphigus.

Brunsting, Goeckerman and O'Leary (5) described lesions occurring in patients with long-standing infection elsewhere in the body. Of five cases which they reported, four had ulcerative colitis and one chronic empyema. The skin lesions were small discreet pustules surrounded by an inflammatory areola. These softened, ulcerated and extended peripherally in a rough serpiginous configuration. The borders were boggy and blue in color. There was extensive undermining and necrosis of the subcutaneous tissue.

In 1933 there appeared a report from the Massachusetts General Hospital (6) of a case of ulcerative colitis with numerous complications including pustular skin lesions. At about the same time Jones (7) described two patients with skin lesions and ulcerative colitis. One, a twenty-six year old male had several areas situated on one arm about an inch in diameter which were red, indurated and tender. There were also smaller nodular lesions elsewhere. Another patient, a 37 year old male, had a pustular skin rash, red papules and small pustules on the pharynx and finally developed an ulceration of the cornea.

Brooke (8), described lesions suggesting an erythema nodosum in a 23 year old female with ulcerative colitis. On various parts of the body, but most marked on the anterior aspect of the legs there were raised tender purplish-blue areas which enlarged and became soft and fluctuant. One of the lesions on the anterior tibia broke down and sloughed, leaving a large ulcerating area over most of the lower leg.

A recent paper by Mackie and Henriques (9) included a brief report of an intensive spreading of skin gangrene of the flank in a patient with ulcerative colitis. Multiple secondary foci surrounded by normal skin appeared.

The following are the five cases to be reported in this paper:

Case No. 1, S. V., a twenty-three year old college student was admitted to the hospital on Feb. 24, 1934, with the chief complaint of severe diarrhea.

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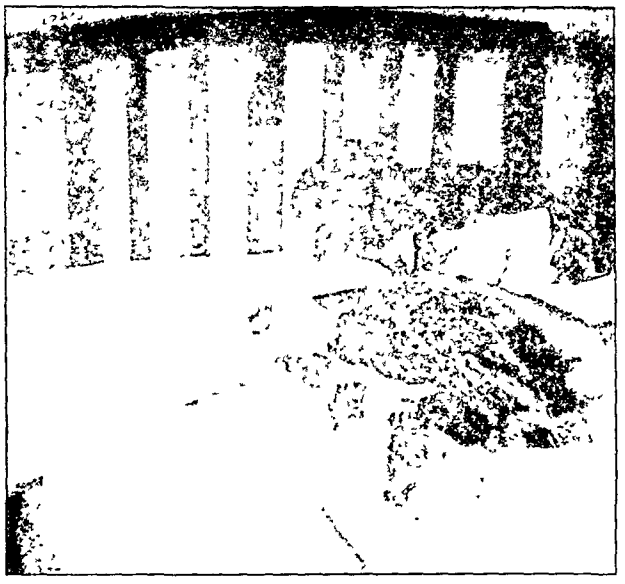


Fig. 1. Picture of the back of Case No. 1. Note the deep and extensive ulcerations of the skin and underlying fascia.

His family history and past history were essentially negative.

About two and one-half years before this admission, he began to have bloody diarrhea which continued intermittently for a period of about six months. A diagnosis of ulcerative colitis was made on the basis of a Roentgen-ray examination and sigmoidoscopy.

About three weeks before admission to the hospital, after a period of almost eight months with fairly normal bowel movements, there was a sudden onset of severe watery and bloody diarrhea, with as many as 15 to 30 bowel movements daily. After being in bed for about two weeks he developed boils which rapidly spread over his back and became particularly severe and painful during his last two days at home.

Physical examination. On admission revealed a fairly well-developed and well nourished young man, apparently very uncomfortable. Over his entire back and to a lesser extent on the upper lateral aspects of his thighs there were numerous furuncles ranging in size from two to four cm. in diameter. Several of these were discharging yellow pus. Examination was otherwise essentially negative.

Clinical pathology. Urine was essentially negative. Stools were liquid and contained occult blood. He showed a moderate secondary anemia. Culture of pus from furuncles showed staphyloccus aureus. Blood culture was negative.

Clinical course. The patient was in the hospital for eighteen days. He continued to run a septic temperature reaching as high as 103 to 104 (by rectum) daily. The diarrhea continued, uninfluenced by diet or medication. Within a few days the furuncles had opened and discharged yellow pus, leaving large ulcerated areas whose borders rapidly spread peripherally so that at the end of a week most of them had become confluent, thus forming very large granulating areas with edges of dirty gray necrotic tissue (Fig. 1). During the last week he was drowsy and at times delirious. Finally, eighteen days after admission there was a sudden rise of temperature to 107, pulse to 180, and respiration to 35, and within six hours he was dead.

Autopsy performed by Dr. M. J. Schlesinger showed the following significant findings: Over the back extending from the level of the seventh cervical vertebra to the iliosacral region and from the posterior axillary line on the left to the posterior axillary line on the right there was an extensive ulcerating granular process with raised irregular and undermined skin edges. Here and there in the center of the process could be seen purplish discolored islands of skin. No pus could be seen either in the form of gross exudate, or in the form of pustules. In the center of the process the ulcerations had extended to the fascia of the muscles, while towards the periphery only the superficial portion of the skin had been affected, the process limiting itself to the corium. At the edges of the lesions were small nodules of purplish necrotic skin.

Similar ulcerating areas measuring 10 to 15 cm. in diameter could be seen over the upper portions of both scapulae and on the lateral aspect of the right thigh separated from the large lesion by an area of intact skin.

Microscopic examination revealed no evidence as to the etiology.

The colon showed the typical chronic ulcerative colitis lesions. No amoebae were found.

Case No. 2, A. S., a 27 year old married business man with an irrelevant family history and a negative past history except for scarlet fever at the age of nine, came to the Beth Israel Hospital on March 4, 1934, with a chief complaint of diarrhea of 2½ months duration. About a month after the onset, he developed on his right leg without apparent cause, a slightly painful sore which failed to heal. For two weeks previous to admission he had fever reaching as high as 102 and a persistent sore throat. The latter caused such difficulty in swallowing that he was unable to take nourishment.

Physical examination revealed a well developed but poorly nourished young man rather pale and moderately sick in appearance. In the right tonsillar region there was a large ulcerated area covered with a greyish membrane. On the calf of the right leg there was a dime sized punched out ulcer, with a slightly raised red margin, extending entirely through the skin into the subcutaneous



Fig. 2. Illustration of a leg of a patient with chronic ulcerative colitis. Reproduced by courtesy of authors from Rankin, Bargen and Buie "Colon, Rectum and Anus." W. B. Saunders Co., Philadelphia.

tissue. The examination was otherwise essentially negative. His blood pressure was 110/80.

Clinical pathology. Urines showed a specific gravity of 1.010 to 1.014 with 0 to slight trace of albumen, 5 to 30 pus cells and 5 to 30 RBC. Blood showed a moderate anemia. Stools were liquid and grossly bloody. No amoebae were found. Blood NPN. was 65. Culture of throat and leg ulcers showed staphylococcus aureus and haemolytic streptococcus. Urine cultures—on two occasions showed staphylococcus albus; on one occasion—no growth. Blood cultures were negative. Culture from ulcer of colon (taken at sigmoidoscopy) showed B. coli, staphylococci, and streptococci.

A diagnosis of ulcerative colitis was confirmed by sigmoidoscopy and barium anema.

Clinical course. Throughout his stay in the hospital the patient had a low grade fever. Two days after admission another ulcer appeared on the buccal surface of the mouth. Because of his painful throat it was difficult to get him to take fluids by mouth. The blood NPN. had risen to 115 and the patient was slightly drowsy. He was given large amounts of fluids under the skin and by intranasal catheter for three days. As a result there was an increase in the urinary output and the throat and mouth lesions became less painful so that he was able to take sufficient fluids by mouth and later a low residue diet. His bowel movements became less frequent, gradually became pasty and contained less blood. The blood NPN. fell; his throat and mouth lesions healed still further, and he felt generally better.

At the time of discharge from the hospital, 23 days after admission, the ulcer on the leg had granulated in very well and was beginning to epithelialize. The mouth and throat ulcerations had entirely disappeared.

Bowel movements were semi-formed, reduced to two daily and no longer contained gross blood although they were still guaiac positive. The blood NPN. had dropped to 29 but the urine still showed albumen, white cells, red cells, and casts. His general condition was markedly improved.

Case No. 3, J. C., a 28 year old printer, in the short period of two and one-half years was admitted to the Beth Israel Hospital five times because of ulcerative colitis and associated complications. His illness began suddenly, early in 1932, with severe bloody diarrhea and abdominal cramps, followed shortly by marked weakness and loss of weight. Because of peri-anal abscesses and persistent activity of his ulcerative colitis, an ileostomy was performed. In February, 1933, he developed superficial furuncles all over his body.

In June, 1933, an abscess formed over the lateral aspect of the left ankle. This was incised and drained at home. It continued to become progressively more painful and swollen so that on July 22, 1933, he was again admitted to the hospital. Local examination showed over the left lateral malleolus and lateral aspect of the left foot a large red hemispherical swelling which was soft, fluctuant and tender. There were numerous small openings which discharged a yellow pus. This carbuncle was incised and warm boric compresses applied. On July 30 the entire surface sloughed away leaving a granulating area 12 cm. in diameter. With saline dressings the granulating area became clean and on August 17, pin point grafts were applied and "took." He was discharged on August 22, 1933.

Six weeks later the swelling of the left ankle recurred and was drained.

Clinical pathology was essentially negative expect for hypochromic anemia.

On November 2, 1934, he was admitted to the Bickur Cholim Hospital for chronic care. While at that institution he developed further abscesses on his feet, associated with an exacerbation of bloody diarrhea and arthritis.

A culture taken from a freshly opened large abscess of his left ankle showed a pure culture of staphylococcus albus. A similar culture takn through a sigmoidoscope from the base of an ulcer in the sigmoid showed the same organism. Therefore, an autogenonous vaccine was prepared and inoculations given. This was followed by striking results in clearing both his skin lesions and his ulcerative colitis symptoms.

Case No. 4, R. L., an eighteen year old girl was admitted to the Medical Service on March 11, 1932, with the chief complaint of intermittent bloody diarrhea and abdominal cramps of one year's duration.

Physical examination was essentially negative except for marked undernourishment and tenderness over the lower abdomen.

A diagnosis of chronic ulcerative colitis was made on the basis of sigmoidoscopic and Roentgenologic evidence.

She remained in the hospital for 5 days and then left against advice.

On June 2, 1932, she was again admitted to the hospital, this time to the surgical service, because in spite of medical treatment the diarrhea and cachexia had become progressively worse. Over the anterior aspect of both feet there were superficial ulcerations—the right about 2x3 cm., the left 4x5 cm. in area. Both were covered by pink granulations.

Her general condition remained poor, in spite of two transfusions. On June 4, 1932, an ileostomy was performed and pin point grafts were applied to the skin ulcerations.

The cutaneous lesions healed, but bloody discharges from the rectum continued. In spite of the well functioning ileostomy her general condition remained extremely poor. Throughout her stay she was uncooperative and unmanageable so that treatment was difficult. On July 26, 1932, she left the hospital once more against advice.

She continued to pass blood and mucus by rectum. On June 5, 1934, 1½ years later, she was seen on the emergency ward where examination showed the same severe emaciation, and a well functioning ileostomy. At that time she again showed some pustular involvement of her ankles.

Case No. 5, L. B., a 43 year old married woman, with an irrelevant family history and past history, was first admitted to the Beth Israel Hospital on December 18, 1933, because of bloody diarrhea of four weeks' duration. She always had had four well formed bowel movements daily. She had fever and lost weight.

Physical examination on admission was essentially negative except for slight pallor.

Sigmoidoscopy showed a marked redness and swelling of the mucous membranes of the rectum and sigmoid. No ulcerations were seen at that time but later examinations showed pin point ulcerations. A culture from one of these ulcers showed staphylococcus albus and B. proteus.

After a 19 day stay in the hospital on a medical and dietetic regime, she had improved sufficiently to be discharged home.

There she did fairly well until September, 1934, when there was an exacerbation of the bloody diarrhea. After this had continued for two weeks, two indurated red areas, about 4 to 5 cm. in diameter, appeared on the right thigh and left buttock, and she had pain on the spine. Ten days later an abscess formed on the dorsum of the right little finger.

She was admitted to the Beth Israel Hospital for the second time on October 8, 1934, and the abscess was incised and drained. Under medical regime the colitis improved. However, the local infection of the little finger persisted and X-ray revealed an osteomyelitis. The cultures of the pus from the abscess showed staphylococcus albus.

DISCUSSION

These five cases have much in common. All occurred in chronic idiopathic ulcerative colitis during the height of an acute exacerbation. All had febrile reaction, were more or less toxic and had an active diar-

rhea with watery stools, containing mucus, blood and pus. The two patients who had an ileostomy showed considerable muco-purulent-sanguinous rectal discharges. In none of these cases could either Bargen's organism or entameba histolytica be isolated. Bacillary dysentery was excluded by negative cultures and specific agglutination tests. Various organisms were cultured in three cases from smears taken from the base of the ulcers in the sigmoid. The organisms cultured were staphylococcus aureus, staphylococcus albus and the hemolytic streptococcus either separately or together, but there is no evidence as to whether these were the primary cause of the lesions or secondary invaders. In two out of three cases the same organisms were found in the skin lesions as in the ulcers of the intestinal mucosa. This suggests the possibility of a metastatic origin of the skin infection. However, we have no proof that metastatic infection has actually occurred in these cases or in any of the cases reported in the literature.

A lowered resistance to infection seems to play an important role in the etiology of these skin ulcerations, whether these are caused by organisms which get into the skin by direct invasion or are carried there through the blood stream from the diseased colon. In those instances in which recovery took place, improvement in the skin ulcerations accompanied improvement of the general condition of the patient.

The skin lesions encountered in these five cases as well as those described in the literature vary a great deal in severity. In some cases they were merely punched out ulcerations or redness, swelling and induration without abscess formation, in other cases there were multiple distinct abscesses. In Case One, as well as in the case illustrated in Rankin, Bargen and Buie's book (Fig. 2) there were deep ulcerations involving a large part of the skin and subcutaneous tissues. It is interesting to point out, that an ileostomy does not prevent any distant skin involvement, provided that the colon infection persists, as it frequently does. The skin infection occurred in Case Three 15 months after an ileostomy and in Case Four—18 months. In both cases infection of the colon persisted in spite of the operation and a colectomy was advised but rejected by the patients. The amount of colon involvement does not seem to bear any relationship to the severity of the skin infection.

The early skin lesions often resemble toxic skin diseases. In the literature we found some references to these manifestations as pemphigus, blebs and erythema nodosum. Their course, however, is not typical and in most cases pyogenic infection occurs.

The treatment of the pyogenic skin infections in the course of an ulcerative colitis is largely symptomatic. Incision and drainage of single abscesses, heat —dry or moist—in the punched-out ulcerations. In the one case in which autogenous vaccine was tried, the results were apparently excellent. When the infection is widespread and deep the management may become very difficult and the prognosis serious. In one case the skin infection was the primary cause of death. The treatment must naturally be directed at the same time to the management of the primary disease, namely the chronic ulcerative colitis. Whatever management will cause a remission of the chronic ulcerative colitis will contribute to the healing of the pyogenic skin infection.

SUMMARY

Five cases of chronic idiopathic ulcerative colitis complicated by infection of the skin are presented. In all cases the skin infections occurred during the height of an exacerbation and in four of the five cases subsided together with the remission of the colitis. One case succumbed to the infection.

The possible mechanisms which play a part in the skin infections during the course of an idiopathic ulcerative colitis, are discussed. The skin lesions as encountered in this series as well as those in the literature are described. The treatment is outlined.

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Is Phenolphthalein Harmful?

By

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IT becomes necessary to discuss this question for the following two reasons: first, because I was the one to introduce phenolphthalein as a laxative; and, secondly, because of the occasional unfavorable reports regarding its use.

Before proceeding any further, I wish to correct the erroneous impression as to the manner in which I came upon the action of this drug. It is stated that phenolphthalein was advocated for the denaturing of wines made from the husks of grapes (artificial wines used by the poorer classes who added sugar water to the pressed husks of grapes and allowed it to ferment), and that diarrhea was then observed following the use of such wines. It is unfair to the Hungarian Govern-

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ment to think that they would have permitted anything to be added to any drink without previously investigating its effect on the health of its people. The Federal Public Health Council has functioned in Hungary since 1876. Every Federal regulation and licensure regarding the use of drugs has to pass through this body, and even to this day the sale of phenolphthalein in the form of chewing gum or candy is restricted to chemists and cosmetic shops, and it cannot be obtained elsewhere. It must be sold in packages accurately labeled as to the active ingredient and the dose. That the laxative properties of this drug could not possibly have been discovered by the drinking of adulterated wines, may be noted from the following. Phenolphthalein turns pink in an alkaline solution even in a dilution of one to ten millions; and, as the amount of phenolphthalein that is needed to detect these wines is infinitesimal (0.1 Gm. to 100 liters), it would be necessary, even if 1 Gm. were used, to drink at least 10 liters of the wine before diarrhea would develop.

When it was proposed to denature artificial wines with phenolphthalein, I was first entrusted with the task of investigating the harmlessness of this reagent. I carried on numerous experiments on animals with negative results. One small pet dog that received 6 gm. of phenolphthalein became quite constipated and passed fecal masses as if it had been fed on a diet of bones, but these fecal masses became crimson on the addition of alkali. Following this, the drug was tried on man. A colleague took 1 gm. and I took 1.5 gm. of phenolphthalein at 11 a. m. The effect appeared between 1 to 3 p. m. that afternoon, in the form of three to five watery evacuations accompanied by some borborygmi. A similar action occurred that evening and also the next morning, but in no way disturbed us from our regular afternoon laboratory work or our night's rest. I became convinced that I had discovered a laxative of great merit. It was easy to take owing to its tastelessness. It did not gripe and did not seem to have any drastic effect even in large doses (1.5 gm.). It was later found that 0.1 gm. taken in the evening emptied the contents of the colon the following morning, resulting in a copious but soft movement. Our clinical co-workers had the same experience with this drug and obtained the same results, emphasizing that they found no contraindications to its use in various organic disturbances, not even in patients suffering from kidney affections. Of particular value was the report of pediatricians that children and even infants reacted well to this laxative and showed great tolerance to it. The pediatricians preferred it to the troublesome castor oil because phenolphthalein was mild in action and pleasant to take. Other clinicians noted that bedridden patients required a greater dose of phenolphthalein than ambulant patients. Febrile patients were more resistant to the action of this drug, owing to the recognized physiological and pathological behavior of the intestinal tract in such states.

I therefore introduced this laxative in 1902 (1) on the basis of animal experiments, on observations on myself and my associates and also on its clinical trial in a great many adults and children. I made the statement then, and I still believe so today, that phenolphthalein is harmless. It has received support from many clinicians who cited their experience in thousands of cases where this laxative was used without any mishap (2). You read in some of the literature that phenolphthalein may cause irritation of the kidneys, yet these observers never noted such ill effects pertaining to the kidneys or any of the other excretory organs. It is a laxative in common use for many years, particularly in the United States, where the sales last year, according to the U. S. Tariff Commission, amounted to 451,418 pounds. This means that several billion doses of phenolphthalein in various preparations, were consumed in 1933 alone. The numerous reports of overdoses with no ill effects (3) also supports my contention of the harmlessness of the drug. Among these will be found an instance where a child, 3½ years old, took as high as 96 grains of phenolphthalein with apparently nothing more than the added purgative action and some slight vomiting (see footnote 3f).

There are about twenty separate instances cited in the literature where some general disturbance has been attributed to the use of phenolphthalein. I consider most of these reports as not definitely proven. Sollman (4) states that the reactions reported by Holz (5a), Best (5b), Zabel (5c) and others, are doubtful in nature. Hydrick (6) detected a transient albuminuria following an average dose of phenolphthalein. Other observers (7) failed to confirm the findings of Hydrick. Assuming that the reported reactions are due to phenolphthalein, it still shows that considering the enormous number of doses consumed, such reactions are so few as to be practically negligible, no more than can be accounted for by an unusual idiosyncrasy of certain individuals.

My endeavors to reveal the mode of action of phenolphthalein were futile, and to this day I can only speak of the probability of one theory. The reason for this is primarily due to the fact that the drug is inactive in animals except with large doses frequently repeated. I did notice purgative effects from phenolphthalein in cats living on a milk diet but these experiments were not conclusive as this occurred in a number of other cats as a result of feeding milk alone. The fact that this drug seems to be effective in man only points to interesting but unexplained differences between the bowel functions of mammals and man. The watery evacuations that follow the use of phenolphthalein in man resemble those produced by salts of low diffusing capacity. This led me to consider the possibility that in the human intestine phenolphthalein forms a sodium salt leading to fluid retention which becomes responsible for the mild laxative effect. Indeed my experiments with diffusion funnels have shown that a 1% solution of the sodium salt of phenolphthalein is capable of holding so much water that the fluid in the diffusion funnel reached the height of 3 meters while the animal membrane bulged considerably downward. After many unsuccessful experiments the 1.25% solution—as computed from the lowering of the freezing point—proved the osmotic pressure to be equal to 1.75 atmospheres.

However, the theory that the mode of action of phenolphthalein was due to the formation of a sodium salt of low diffusion properties, could not be maintained in view of the fact that small doses of the drug

were effective. Such great molecular action could not be expected from such minimal amounts. Furthermore, although the drug has been in use for many years, examinations of the small intestinal contents of man at autopsy, have never revealed them to be of a pink coloration, nor could this be observed in any of my experimental animals. This, however, can be explained because the alkalinity of the small intestine is not due to a strong alkali but to sodium bicarbonate. Its absorption amounts to very little, for 87% of the drug was recovered from the feces of a dog which had received 3 gm. of phenolphthalein.

The question has been raised, does phenolphthalein injure the liver? This originated with Dr. F. J. Cullen, formerly director of the U. S. Federal Food and Drug Administration in Washington, who accuses phenolphthalein of causing injury to the liver tissue. I have never read or heard of such an effect on the liver, and assumption is far from proof. On the contrary, several investigators have used the drug in patients with acholic stools and have found its action favorable (8). Cases have been reported where the halogen compounds of phenolphthalein used in roentgenography of the gall bladder—tetraiodophenolphthalein, phenoltetrachlorphthalein, tetrabromphenolphthalein—have caused injury to the liver. Some of these have laxative action but cannot be considered in the same light as phenolphthalein, from which they differ chemically. It is certain that the reports of injury to the liver produced by the halogen compounds, have been confused and wrongfully attributed by Dr. Cullen to phenolphthalein.

Phenolphthalein acts as a laxative but is of no value for any of the diagnostic procedures for which the halogen compounds are used. Practically ninety per cent of phenolphthalein is immediately excreted with the intestinal excretions. The drug cannot be detected three or four days after ingestion. The rare instances in which a reaction occurs may only be due to the comparatively small amount of the drug that is absorbed, which either induces sensitization or else produces symptoms in one already sensitized. There is reason to believe that the small amount of phenolphthalein absorbed is converted into a conjugate, probably a sulpho-compound. If so, it is harmless because another sulpho-derivative of phenolphthalein—phenolsulphonephthalein—is being used intravenously as a kidney function test, and so far no ill effects have been noted following its use.

Phenolphthalein has established itself as a useful laxative. Its effect is limited to the intestinal tract. It has found its way into every pharmacopoeia and various other medical texts, but in none is it listed as a poisonous drug. Its popularity is reflected by the numerous laxatives, digestive mixtures, cholagogues, etc., on the market, containing phenolphthalein. I derive great satisfaction in contemplating the benefit that physicians have achieved with this drug in patients. When one compares the few "reactions" reported with the countless instances in which the drug is used without any ill effects, such "reactions" must be considered mostly as pure coincidences. No one should take the reports of such ill effects seriously unless they are unqualifiedly proven.

The most characteristic example of a fortuitous "reaction" is that recently reported by Cleeves (9), who observed the death of a boy 10 years old, following the taking of an overdose of phenolphthalein. I will include here the clinical history and post-mortem findings of this case in full, in order to present a clear view of the entire case.

One-half box (1.15 Gm. of phenolphthalein) of the well-known American purgative, Ex-Lax tablets, was taken by a ten-year old boy. A copious diarrhea developed which passed off without trouble and without any medication. The following day the temperature rose to 41° C. and because of this Dr. Cleeves who was called, prescribed bismuth powders. The boy felt much better on the next day of his illness but owing to the continued fever, another physician was called, who prescribed sodium salicylate. The boy's pulse was 130. The fever persisted and on the fifth day a sudden eruption of huge wheals with sharply marginated serpiginous borders developed on the abdomen, legs and arms, and lasted for twenty-four hours. On the sixth day of illness, hemiplegia was noted and the child became delirious. Multiple petechiae appeared on the abdomen and subcutaneous hemorrhages developed on the feet. The fever remained at 40° C. Coma finally supervened, with gradual failure of respiration, and the child died on the ninth day after taking the laxative. His urine was examined repeatedly and remained normal until the last day when blood appeared in it.

No stool or blood studies or histological examinations of the skin lesions, nor a chemical examination was made during the boy's illness or after death. At the post-mortem, a great many hemorrhages were found in the intestine as well as in all organs such as the kidney, liver, brain, meninges and cardiac muscle. Infarcts were noted in the aortic valves. The spleen was four times the normal in size, soft, dark red, and the adrenal glands were almost liquified. In the right island of Reil of the congested brain, a large size hemorrhage was visible which was probably the cause of the hemiplegia. The pathological picture was that of a systemic vascular disease.

Any one who reviews this clinical history and post-mortem findings with careful attention to all the details in this case, would immediately see that the condition had nothing whatever to do with the drug and that one is dealing here with a severe toxic effect, the latent period of which happened to coincide with the taking of Ex-Lax tablets. How and when this toxin entered the body of this previously perfectly healthy boy and what the nature of this cellular poison could be, whether it was ingested in the form of bacteria or spoiled food, cannot now be proven. Perhaps it could have been revealed by a more careful study at the time of illness or immediately after death. The cause of death was rather hastily ascribed to "acute enterocolitis due to the eating of Ex-Lax tablets." Others have referred to this case as it is so on record, although a perusal of the original report shows that the cause and effect is by no means definitely established. The evidence submitted is the post hoc ergo propter hoc kind and therefore open to the just criticism that such observations merit.

I have included the rather detailed report of this unusual case of Cleeves only to prove my own arguments. I do not believe that there will be even a single colleague among my readers who will be willing to see in this case, any connection between phenolphthalein and the febrile hemorrhagic toxic effects described by Cleeves. Moreover, I am convinced that my colleagues who have used phenolphthalein on any number of occasions with absolute satisfaction read this article in America with the same criticisms that I have made

and confidently continue to prescribe phenolphthalein without hesitation.

The report of this fatal case appeared opportunely for Dr. F. J. Cullen, formerly the Director of the Federal Food and Drug Administration of the Department of Agriculture, in Washington, who is striving to restrict the public from the use of laxatives and other drugs, no matter how harmless they may be, when put up in the form of candy or chewing gum. As I mentioned before, I share entirely Dr. Cullen's viewpoint according to which it is a fact that there is no possible, logical excuse that patent medicines (specialties) should be put up in misleading candy form and should be available for sale to the public without differentiating medicine from candy. But I am sorry that in his fight for this principle, he declares war only on phenolphthalein and after citing all the incriminating data including the Cleeves case, he finally ends by stating that it is generally known that phenolphthalein has a well recognized injurious effect on the liver. The latter statement has no foundation in fact. No purpose will be achieved by exaggeration or distortion of the truth. One defeats the very aims desired to be attained by such methods.

This review will be incomplete if I should fail to mention the reliable observations which seemingly indicate that very occasionally certain individuals have an allergic hypersensitiveness to phenolphthalein. This hypersensitiveness usually manifests itself in a mild skin eruption (Abramowitz (10a), Wise and Abramowitz (10b), Ayres (10c), Corson and Sidlick (10d), Rosenbloom (10e), Ely (10f)). Such observations have been made since 1918 following the extensive investigations of Storm VanLeeuwen on allergy and asthma which stimulated further work of this sort in the United States. In later years reports of skin eruptions from phenolphthalein have appeared from various parts of Europe and recently our own Dermatologists have encountered instances of this sort which altogether may be considered rather rare and nothing more than a curiosity. These are considered idiosyncrasies and they are of no more significance than those idiosyncrasies brought on by berries, lobsters, sweet cream, pollen, chicken feathers, horse hair mattresses, etc., which certain individuals cannot tolerate. We also sometimes find patients who possess an idiosyncrasy to drugs like aspirin, bromides, digitalis, iodides, ipecac, and the antipyretics and analgesics, but who would even think of giving up these valuable drugs for that reason?

I owe this short critical review of the reports emphasizing the harmful effects of phenolphthalein to my colleagues and my conscience because I have been responsible for its world wide usage. I have no intention of showering phenolphthalein with undeserved praise. The many publications which have approved the use of this drug on the basis of innumerable and careful clinical observations support my contention that phenolphthalein is harmless. In view of the popularity of phenolphthalein this is really unnecessary, yet it is my desire that my colleagues should be convinced of the harmlessness of phenolphthalein, as a am. They should receive reports of the ill effects of this drug that are based on post hoc ergo propter hoc reasoning with scepticism and form their opinions based on their own experiences and on those of other reliable investigators, as befits independentiy thinking physicians.

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SECTION II—*Experimental Physiology*

The Prophylactic Value of Gastric Mucin in the Therapy of Post-Operative Jejunal Ulcer:
An Experimental Study in Dogs

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IN this paper, the authors will report the results obtained on the prevention of the occurrence of jejunal ulcer in dogs when operated according to the method of Exalto (1) and Mann and Williamson (2). This method involves an end-to-end gastro-jejunostomy, and the diversion of the pancreatic juice and bile into the last twelve inches of the ileum. This method was chosen, first, because from 95 to 100 per cent of dogs so operated develop jejunal ulcers, and second, because of this regularity of occurrence of ulcer, positive results obtained by a therapeutic procedure would have more significance. The prophylactic therapeutic agents employed were (a) gastric mucin, (b) alkalies, (c) a mixture of gastric mucin, alkalies and raw ground pancreas. Experiments have also been made in which the effect of gastric mucin and raw ground pancreas on the healing of an ulcer after its development was studied. The results of gastric analyses, hemoglobin and plasma bicarbonate determinations will be reported.

CONTROL EXPERIMENTS

It should be borne in mind that the diversion of the bile and pancreatic juice into the lower ileum *per se* produces a marked disturbance of digestion and the large majority of animals so operated lose considerable weight and require special care in regard to hygiene and nursing.

The animals in this series of studies were kept in cages usually containing excelsior bedding and were fed a diet of ground meat, either fresh or brought to the boiling point (chiefly the latter) as preferred by the individual animal, and milk. The animals were fed three times daily, some eating all the food within a short period, others eating throughout the day. The stomach tube was not used on any of the control dogs, but it was frequently used to administer therapy in the treated dogs.

Mann (2) reported the jejunal ulcers develop in dogs prepared by his method in from three weeks to four months post-operatively, the average time being about one month. He did not cite specific data, but he stated that from 90 to 95 per cent of the dogs develop ulcer. Morton (3) observed that all of twenty dogs similarly operated developed ulcer in from fourteen days to four months. Owings and Smith (4) found that ulcers occurred in all of ten dogs in from forty-two to 428 days, the average being 118 days. L. R. Dragstedt (5) found that ulcers occurred in six dogs in from twenty-six to sixty-one days, the average being thirty-nine days.

Since the hygiene and diet of dogs operated on according to the method employed may be of some significance, it was thought best to operate a control series and determine the occurrence of jejunal ulcer on our diet and under our laboratory conditions. We should add that in every dog operated the duodenum was anastomosed to the ileum 12 to 15 cm. proximal to the ileo-cecal sphincter.

Accordingly, forty-two healthy dogs were operated and used for untreated controls. (If the dogs are prepared properly before the operation, the immediate mortality of the operation is practically zero). In all of the forty-two untreated control dogs, jejunal ulcer was found at death in from fourteen to 120 days post-operatively, the average being seventy-eight days.

In order to use the data obtained on the control dogs more effectively and to compare, *vide infra*, the data obtained in the control group with that of the treated groups, curves A and B in Figure 1 were constructed. Curve A represents the percentage survival-time curve of the forty-two untreated control dogs with a Mann-Williamson operation, all dying with ulcer but not always directly due to the complications of ulcer. For example, referring to Curve A, it will be noted that 50% of the dogs had died with ulcer at 11 weeks. Curve B represents the time of diagnosis of ulcer in twenty-two of the dogs. For example, referring to Curve B, it will be noted that 50% of the dogs had developed ulcer at 7 weeks. The diagnosis was made on the basis of "tarry stools" or gross blood in the gastric analysis; in eight the diagnosis of ulcer was confirmed by surgical exploration. These curves will be used later to interpret the data or the prophylactic effectiveness of the therapeutic measure employed.

GASTRIC SECRETORY AND BLOOD STUDIES

It was obviously important to possess knowledge concerning the effect of the operation on gastric secretion and emptying time. In addition, since the alkaline juices were being passed into the ileum near the colon,

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they would be more subject to loss from the body. Thus, it was considered important to follow the alkaline reserve in a group of the animals. Hemoglobin and hematocrit determinations were also made.

McCann (6) seems to have made the only study to determine whether or not gastric acidity is influenced by the Exalto-Mann-Williamson operation, or to determine whether the ulcer is due to an acid chyme of normal or hypernormal quantity and quality. By a method of fractional gastric analysis, he measured the effect of the Mann-Williamson operation on the acidity of the gastric contents during digestive activity and during rest. He reported that there was no essential alteration in the character of the curves of the acidity of the gastric contents in response to the test meal after the Mann-Williamson operation, and concluded that "these ulcers have occurred with the passage of chyme of normal acidity." Yet, during the stage of ulcer formation, he noted the development of an increased quantity of resting basal secretion, and a post-operative impediment to emptying. Morton (3) also found by roentgenologic study that there was a slight stasis during the first two weeks after operation and that this subsequently increased. We considered McCann's work incomplete and desired further information.

Outline of methods. Dogs in this experiment were carried through three stages, namely, before, during, and after experimental induction of jejunal ulcers. In the first stage, control values were established for the following tests: the acidity of the gastric contents in response to a meal, the carbon dioxide combining power of the blood plasma, the red corpuscle and plasma volume, and the weight. The dogs were then subjected to the operation, which produces ulcer in 95 per cent or more of dogs, and were thus in the stage during ulcer formation. During this stage, further determinations of the values for the above tests were made. After the diagnosis of ulcer was made, either by surgical exploration, or clinical and laboratory observations, the dogs were in stage 3, or that after development of ulcer.

The various determinations were continued during the stage, in which *treatment was given.* Complete autopsy records were made at death or after etherization.

Explanation of experimental methods. The acidity of the gastric contents after a standard meal was determined by withdrawing through a large stomach tube a sample of gastric contents, at 2, 4, and 6 hours, or longer, after the feeding. The standard meal consisted of 200 c.c. milk, 100 gms. of finely ground meat and 50 gms. of finely ground raw pancreas. The test meal was always given after 10 hours of fasting to insure an empty stomach, *i.e.*, in the morning at eight o'clock. Free acid was determined by titrating against N/40 NaOH using dimethylaminoazobenzene as an indicator, and total acid by using phenolphthalein as an indicator. The response to the meal before operation was determined on 4 to 8 different, generally consecutive, days. The carbon dioxide combining power of the blood plasma was determined by the Van Slyke method. The red corpuscle count and plasma volumes were determined from the hematocrit reading made on the blood drawn for the carbon dioxide determination. The body weight was recorded at various times throughout the entire experimental period.

The operation was then performed, and from 10 to 12 days of post-operative convalescense were allowed before the daily test meals and aspiration of samples were resumed.

During the period of treatment, the acidity of the gastric contents in response to the test meal was recorded in the following manner. The 7:00 a. m. and subsequent mucin feedings were omitted; the meal was fed at 8:00 a. m., and aspiration of samples of stomach contents made at 10:00 a. m., 12:00 noon, and 2:00 p. m. Following the last aspiration, unless others were made, the dog was given the regular mucin-alkalie-raw pancreas feeding, and the cooked meat, and the schedule of three or four times daily feedings was recommenced.

During the control period before operation, aspiration was difficult, due to the lack of appreciable fluidity of the gastric contents. The stomach emptied between four and six hours after the meal. After the operation, however, all aspirations were easily accomplished and were productive of large amounts of non-viscous fluid containing a heavy suspension of fine particles. Over 200 c.c. could often be aspirated at 4 hours, and most always at 6 hours.

TABLE I

Averages of All Dogs

	Average Acidity					
	Free			Total		
Hours p.c.	2	4	6	2	4	6
Procedure						
1. Control	.028	.101	.132	.323	.357	.369
2. After operation No treatment	.051	.107	.136	.328	.369	.361
3. After ulcer diagnosed a. At Exploration	.056	.150	.203	.372	.394	.378
b. By Observation	.036	.100	.149	.320	.353	.340

Weight loss and appetite. During the post-operative period, the dogs manifested marked polyphagia, eating very rapidly much larger quantities than normal dogs of the same size. We presented all the food they could eat. However, the dogs lost on the average one-third (31 per cent) of their body weight between the time of the Mann-Williamson operation and autopsy. Eighty-four per cent of this loss had occurred by the time the diagnosis of ulcer had been made. Forty-five per cent was in the first 17 days after operation, which was 35 days before the average time of development of ulcer and was 7 days before the earliest ulcer formed in this group, which was one diagnosed by exploratory at 24 days. Thus, one-half the weight loss occurred in the first 2½ weeks, before any ulcers were present, and four-fifths by the time the ulcer had developed. This furnishes ample verification for the statement (7) that Mann-Williamson operated dogs have a marked nutritional disturbance.

Acidity averages. The acidity averages for all twenty-two dogs, based on 444 test meals and 2,664 titrations, are found in Table I, which is constructed on the basis of values for the individual dogs given in Tables II and III. The graphic representations of curves for these average values (Figure 2) show more or less post-operative increase in both free and total acidity at each of the three aspirations during the 6 hour period of observation. A relatively higher 2 hour free acidity distinguished the post-operative free acid curve from the closely parallel control.

Post-operatively, the gastric contents have a higher total acidity, which continues for a greater period of time.

After diagnosis of ulcer by exploration (8 dogs, Table X), even though treatment was given, the average acidities, both free and total, were distinctly higher (Figure 2, Curve 3). This must have been due to the operation. The jejunotomy must have caused increased local irritation and consequently greater retention of secretion. In the dogs where ulcer was diagnosed by observation, and the treatment started,

the acid values are lower (Figure 1, Curve 4). The 6 hour acidities show the greatest differences; at this aspiration, the free acidity exceeds that of the control and of the post-operative periods.

Individual acidity averages. From a study of the individual dogs, it is evident that in each dog the secretion might post-operatively remain unchanged, or exhibit any one of four possible variations in gastric secretory response. About 50 per cent of our dogs showed a post-operative increase in both free and total acidity. Only one dog (No. 13) showed a post-operative fall in both free and total acidity.

The increased "continuous phase" of gastric secretion was very evident and marked which confirms Mc-Cann. This and the very evident fluidity of the gastric contents leads us to conclude that following the operation a greater volume of secretion was produced. This was true of every dog regardless of the acid values.

The results of the study of hemoglobin and hematocrit determinations revealed that an anemia does not appear until the ulcer starts to bleed. This was true without a single exception. This shows that anemia is not the cause of the ulcer. The response of the dog to therapy was directly reflected by a rise in hemoglobin and hematocrit. The hemoglobin would rise and remain high during the chronic stage of ulcer, until bleeding started again. This was true of all dogs shown in Table XI. Perforation would occur in the presence of normal hemoglobin and hematocrit values.

Observations on Plasma CO_2 Combining Power: The control values for the plasma bicarbonate reserve varied from 48 to 55 per cent. From one to six weeks post-operatively every dog showed a decrease in plasma alkaline reserve, the values ranging from 30 to 48. About one-third of the dogs showed a gradual decline, the others fluctuated considerably. When hemorrhage started the drop was increased. During the week before starting mucin-alkaline-pancreas therapy, the values ranged from 29 to 48, the average being 37. On therapy the plasma bicarbonate was increased to or above normal, none rising above 68. The plasma bicarbonate would then fall depending on the amount of hemorrhage; only one dog fell below normal, however.

No correlation existed between the post-operative rate of fall of blood alkaline reserve and the rate of development of ulcer, although these determinations were made primarily to detect such a correlation. Such a correlation might have been possible, if fluctuations had not occurred to the extent observed. These fluctuations may have been due to either variations in the amount of pancreatic and biliary alkalie lost in the feces or to variations in blood loss which was not determined accurately (in view of the diet accurate loss

TABLE II

Acidity Averages

Dog No.	Control Free Hours after meal 2	4	6	Control Total Hours after meal 2	4	6	After Mann-Williamson operation Free Hours after meal 2	·	6	After Mann-Williamson operation Total Hours after meal 2	4	6
1	.054	.154	.068	.226	.280	.119	.044	.128	.137	.333	.392	.319
2	.030	.150	.101	.256	.320	.213	.065	.159	.175	.343	.389	.377
3	.010	.095	.057	.156	.275	.191	.039	.090	.138	.293	.354	.386
4	.0	.069	.129	.297	.320	.338	.030	.111	.168	.348	.386	.401
5	.0	.089	.118	.337	.402	.278	.015	.114	.127	.373	.407	.389
6	.018	.106	.117	.355	.324	.271	.022	.062	.167	.346	.346	.346
7	.048	.148	.169	.359	.333	.286	.100	.144	.154	.354	.373	.322
8	.015	.094	.191	.361	.372	.384	.0	.042	.115	.352	.436	.461
9	.051	.123	.136	.359	.394	.349	.071	.139	.169	.346	.389	.388
10	.021	.097	.111	.359	.406	.351	.094	.133	.117	.309	.342	.286
11	.029	.076	.124	.275	.277	.288	.079	.131	.131	.321	.356	.345
12	.045	.117	.159	.309	.388	.312	.052	.128	.145	.319	.373	.345
13	.026	.139	.156	.397	.429	.352	.046	.098	.129	.321	.343	.348
14	.019	.064	.141	.301	.481	.414	.054	.088	.148	.303	.373	.419
15	.146	.150	.168	.389	.339	.314	.065	.127	.157	.288	.355	.347
17	.048	.099	.122	.297	.344	.330	.026	.079	.122	.303	.353	.339
18	.010	.098	.118	.329	.446	.366	.048	.086	.126	.301	.364	.354
19	.0	.080	.122	.281	.326	.376	.048	.090	.112	.348	.409	.380
20	.0	.082	.156	.269	.291	.270	.055	.097	.127	.294	.338	.309
21	.010	.074	.123	.335	.388	.356	.072	.100	.163	.364	.337	.369
22	.018	.074	.197	.347	.363	.349	.052	.108	.138	.322	.344	.351
Combined Average	0.028	0.104	0.132	0.323	0.357	0.309	0.051	0.107	0.136	0.328	0.369	0.361

TABLE III

Average Acidity After Diagnosis of Ulcer at Exploratory Operation and Gastric Mucin Treatment

Dog. No.	Free Hours after meal 2	4	6	Total Hours after meal 2	4	6
3	.036	.103	.174	.352	.365	.333
4	.067	.192	.255	.386	.403	.396
5	.033	.139	.216	.378	.432	.423
7	.109	.134	.167	.332	.334	.297
8	.036	.183	.205	.412	.438	.422
Average	0.056	0.150	0.203	0.372	0.394	0.378

Average Acidity After Diagnosis of Ulcer by Clinical and Laboratory Examination and Mucin and Alkali Treatment

Dog No.	Free Hours after meal 2	4	6	Total Hours after meal 2	4	6
9	.009	.060	.115	.328	.359	.368
11	.077	.176	.188	.282	.339	.368
12	.068	.129	.205	.325	.357	.357
13	.008	.076	.130	.321	.341	.329
14	.018	.127	.158	.342	.389	.344
15	.028	.062	.139	.308	.335	.345
17	.043	.088	.133	.330	.334	.364
19	.043	.084	.125	.328	.366	.312
Average	0.036	0.100	0.149	0.320	0.353	0.340

of blood in the feces could not be determined) and daily.

DISCUSSION

Although the free and total acidity was more or less definitely increased in one-half the animals, the most striking finding resulting from the gastric analysis is the failure of the total acidity to fall at the six hour period, as in the controls, and the hypersecretion of fluid of high acidity. This did not occur just before the development of the ulcer, but after the operation, and was not affected by the presence of ulcer; nor was it materially influenced by our therapy. We believe that the varying degrees of hypernormal acidity observed in about one-half of the dogs was due chiefly to retention. But, the hypersecretion of fluid observed especially at 4 and 6 hours after the meal and which continued afterwards, as observed by McCann, is of special interest and we believe bears on the etiology of the ulcer that results.

TABLE IV

Effect of Gastric Mucin and Alkalies on the Rate of Gastric Emptying Time. (Constituents of each meal are given in the text)

	Emptying time average of 4 or more tests			
Dog	Meal 1	Meal 2	Meal 3	Meal 4
I	4 hr 40 m	4 hr	4 hr	3 hr 30 m
II	4 hr 25 m	4 hr	4 hr	3 hr 40 m
III	4 hr 45 m	4 hr 5 m	4 hr	3 hr 40 m
IV	4 hr 15 m	4 hr	3 hr 50 m	3 hr 30 m

A discussion of the quality of the excessive fluid secretion and the mechanisms concerned in its formation is hardly warranted in this paper (see Ivy, ref. 8), but preliminary studies indicate that it is not materially influenced by relatively large doses of atropine. If this proves to be correct, it means that the mechanism concerned is not one of the normal mechanisms for gastric secretion in the dog, all of which are depressed by atropine. The most likely hypothesis is that the irritation of the upper intestinal mucosa may result in the elaboration of histamine-like substances which on absorption stimulate gastric secretion of HCl and fluid, and prolong the intestinal phase—an abnormal mechanism that would not be influenced by atropine except in toxic doses.

SUMMARY

1. Following the Mann-Williamson operation for duodenal drainage, there occurs an increase in both free and total average acidities in about one-half of the animals. In the others the acidity is not significantly altered. Gastric retention is present after the Mann-Williamson operation and is at least partly responsible for the early increase in free acidity. A marked increase in the intestinal phase of gastric secretion and in the continuous secretion occurs which unbuffered has a deleterious action to the especially susceptible jejunal mucosa (6, 7). There is no correlation between the time of ulcer appearance and the acidity. The nutritional or digestive disturbance in Mann-Williamson dogs is severe as shown by the excessive weight loss before development of ulcer. The acidity rises above the original post-operative level after exploratory diagnosis of jejunal ulcer and institution of gastric mucin treatment. The acidity falls below the original post-operative level after clinical and laboratory diagnosis of jejunal ulcer and institution of mucin and alkali treatment, but the change is not marked. The observations recorded on plasma bicarbonate reserve and on anemia in the Mann-Williamson preparation show that these factors play no definite etiologic *rôle*.

EFFECT OF GASTRIC MUCIN AND ALKALIES ON THE GASTRIC EMPTYING TIME OF DOGS

It was pertinent to these studies to obtain some idea of the effect of gastric mucin and alkalies on the emptying time of the stomach in the dog. It was shown that when gastric mucin was mixed with milk and then the milk clotted with rennin the resulting clot was less firm. This effect of mucin should, of course, facilitate the evacuation of milk from the stomach. This effect of mucin on the clot is shown by many substances, saliva, malted milk, certain mineral salts, etc.

Four normal dogs were selected and trained to lie quietly on the fluoroscopic table. The emptying time to the following test meals was followed: Meal 1: 150 c.c. milk, 25 gm. of finely ground meat, 30 gm. peptone and 35 gm. of barium sulphate. Meal 2: Same as Meal 1, except 30 gm. gastric mucin was substituted for the peptone. Meal 3: Same as Meal 1, except 1 gm. each of calcium carbonate and sodium bicarbonate were added. Meal 4: Same as Meal 3, except 2 gm. of each of the alkalis were used.

TABLE V

Showing the Effect of Gastric Mucin on the Incidence of Jejunal Ulcer After the Method of Exalto, Mann and Williamson. (Incidence of ulcer in these dogs is from 95 to 100%, the latter figure being obtained in control group of 42 dogs)

	Stock diet (see text)			
Dog	Mucin Dosage Ounces	Ulcer	Survival Time Weeks	Remarks
5	2, t.i.d.	None	10	Dog accidentally killed, % body weight lost, 16%.
6	2, t.i.d.	Perforated Ulcer	12	No loss of weight.
7	2, t.i.d.	None	8	Loss of weight, 25%.
9	3, t.i.d.	None	14	Loss of weight, 25%.
10	4, t.i.d.	Ulcers	10	Loss of weight, 33%. High grade pyloric stenosis hemorrhage.
11	1.5, t.i.d.	None	9	No loss of weight—pneumonia.
12	1.5, t.i.d.	None	12	Loss of weight, 25%. pneumonia.
13	1.5, t.i.d.	None	14	No loss of weight cause of death not determined.
14	2, b.i.d.	None	7	Loss of weight, 33%.
16	2, b.i.d.	Ulcer, perforated	9	Slight stenosis.
17	2, b.i.d.	Ulcer, perforated	10	Loss of weight, 16%.
18	2, b.i.d.	No ulcer	8	Ascites, adhesive peritonitis.
19	1.5, b.i.d.	Ulcer, perforated	11	Adhesions, obstructive jaundice, loss of weight, 33%.
20	1.5, b.i.d.	Ulcer, perforated	18	No loss of weight—pneumonia.
21	1.0, b.i.d.	None	52	Explored at 12 months; no ulcer. Taken off mucin. Died of perforated ulcer in 5 months.
22	2, b.i.d.	None	52	Explored at 12 months; no ulcer. Taken off mucin. Died of ulcer in 3 months.
16		6 had ulcer	Avg. 16 wk.	Occurrence of ulcer, 37%. Curve A. Prophylactic value, 35+%.

First four dogs omitted because they received only 0.50 oz. of mucin t.i.d., all dying of ulcer in from 4 to 11 weeks. Dog 8 and 15 omitted because they died without ulcer at 3 and 4 weeks post-operatively. + Calculated by Curve B, figure 1, the prophylactic value is 53%.

One gram of calcium carbonate and sodium bicarbonate each mixed had the same acid buffering value as 30 gm. of the mucin used.

The results are shown in Table IV. The results are obvious and require no discussion.

TABLE VI

Showing Occurrence of Ulcer in Mann-Williamson Dogs on Alkalies. (The doses of alkalies were equal to or greater than the buffering value of mucin given in other series)

Dog	Duration	Ulcer Incidence	Remarks
I	16 weeks	Two jejunal ulcers present. One perforated into omentum 2 cm. in diameter.	Diagnosis of ulcer made at end of 13th wk. Lost ½ body weight.
II	25 weeks	One large indurated jejunal ulcer. Non-perforated.	Lost ½ body weight. Hemorrhage.
III	7 weeks	Two jejunal ulcers present.	Lost ½ body weight. Hemorrhage.
IV	7 weeks	No ulcer present. Cause of death marked enteritis, of unknown cause.	Blood in stool. Lost ⅓ body weight.
V	9 weeks	Acute jejunal ulcer 1 cm. in diameter present.	Lost ½ body weight. Hemorrhage.
VI	11 weeks	Two jejunal ulcers present. One perforating ulcer 1 cm. in diameter which occurred approximately 3 cm. from the anastomosis.	Lost ⅓ body weight.

Alkali Therapy Used

Dogs I, II, III and IV received 2 grams of sodium bicarbonate and 2 grams of calcium carbonate (total of 4 grams) twice a day throughout the entire course.

Dog V received 4 grams of the mixed alkalies twice a day for the first six weeks, then 2 grams of the mixed alkalies twice a day for the last three weeks.

Dog VI received 4 grams of the mixed alkalies twice a day for the first five weeks, then 2 grams of the mixed alkalies twice daily for the last six weeks.

GROUP TREATED WITH GASTRIC MUCIN

In Table V are shown the data on 22 dogs which were operated and then placed on gastric mucin several days later. Since it was not known at first what dose of mucin to use, it is to be noted that the dose was varied somewhat. Of the 22 dogs on mucin, only 6 (or 45 per cent) developed ulcer. If the first four dogs on the small dose of mucin are omitted, and two which died without ulcer at 3 or 4 weeks post-operatively, then ulcer occurred in only 6 out of 16 animals, or 37 per cent. The average length of life of the 6 dogs dying with ulcer is 82 days. The average length of life of the 10 dogs that did not develop ulcer is 131 days. All the 10 dogs, except 3, died without ulcer within a period during which ulcer developed in the control dogs. So, gastric mucin administration in the larger doses kept 10 dogs, or 63 per cent, free from ulcer for an average of 131 days. Life was continued beyond the average for the control group in only 7 dogs. Thus it becomes evident that the operation *per se* in the presence of therapy has a latent mortality of 63 per cent. That is, dogs so operated may live a number of weeks and *die without a jejunal ulcer when given gastric mucin.* This mortality is due chiefly in our experience to a marked disturbance of digestion intercurrent infection, adhesions, intra-abdominal strangulation, etc.

A mathematical treatment of the data in this group is necessary because some dogs may live a considerable period without developing ulcer and others may have developed ulcer had they lived longer. Hence, it was necessary to determine in the case of each dog that died without ulcer, the chance that ulcer should have been present at death. For example, Dog 5, Table V, died at ten weeks without ulcer. Turning to Curve A, Figure 1, it is seen that at ten weeks, the chance of the dog having an ulcer at death is 40 per cent. When the chance is determined for each of the sixteen dogs, assigning zero prophylaxis to the ulcer dogs, and then totaled and averaged, it is found to be 35 per cent, which obviously is more nearly the correct evaluation of the prophylactic effectiveness of mucin *in this group of animals* than the 63 per cent value indicated on a superficial study of Table V. However, it is believed that the figure of 35 per cent represents a minimum figure, since if the truer Curve B of Figure 1 were used instead of Curve A, a larger per cent than 35 would be obtained, namely 53 per cent. The most striking result, however, is shown by the records of dogs 21 and 22. These dogs survived one year without developing an ulcer and then died of ulcer after withdrawing mucin therapy.

It is concluded that gastric mucin when fed in adequate amounts at least delays the onset of ulcer in some dogs and prevents its development in an occasional dog.

ALKALIES

To determine if gastric mucin was producing its effect by buffering free acid, alkali was administered in the food (twice daily) in quantities sufficient to equal at least the buffering value of the mucin given in the other groups. Except as noted in Table VI, 2 grams of sodium bicarbonate and 2 grams of calcium carbonate (total, 4 grams) twice daily was the dose of alkali used. No attempt was made to maintain the gastric contents neutral, as this was not the object of

TABLE VII

Results of Mucin-Alkali-Raw Pancreas

Dog No.*	Wt. at Operation lbs.	Wt. at Autopsy or Now	Survival Time Wk.	Ulcer	Remarks
1	25	15	5	None	Low grade peritonitis.
2	23	15	24	Ulcer	Chronic ulcer resected. New anast. made. On therapy, dog died 21 da. perf. ulcer.
3	26	16	25	Ulcer	Hemorrhage from chronic ulcer.
5	16	14.5	6	None	Liver abscess, unknown etiology.
6	23.5	20	9	None	Low intestinal obstruction due to adhesions.
7	20.5	28.5	3 yr. 9 mo. Still alive	None	Was taken off mucin and alkali one year ago and has not developed an ulcer. Still alive at 3 yr. and 9 mo.
8	22	19	8	None	Adhesions, obstruction.
9	41	38	6	None	Died suddenly from no detectable cause after thorough autopsy.
11	20	30	3 yr. 9 mo. still alive	None	1 yr. ago taken off of mucin and alkali. *Developed ulcer* in 5 mo. Ulcer healed on resumption of mucin and alkali. Still alive 3¾ yr.
12	24	34	52	Ulcer	Chronic ulcer-hemorrhage.
13	25	19.3	10	Ulcer	Perforated.
14	24	24	36	None	Intussusception.
16	32	22	15	None	Pneumonia.
19	14.5	14.5	13	Ulcer	Pneumonia.
22	19	15	12	None	Exploratory—post-operative pneumonia.
15			++	5 ulcers	Occurrence of ulcer 33⅓. Curve A, prophylactic value, 57%+.

*Four dogs are omitted which died at 3 and 4 weeks post-operatively of pneumonia without ulcer.

+ Calculated by Curve C, prophylactic value is 70%.

++ Average does not mean much because of dogs 7 and 11.

this group of six experiments. It might be pointed out that one gram each of the alkalies used twice daily is sufficient to neutralize 638 c.c. of N/10 HCl. The results are recorded in Table VI.

Five of the six dogs died with ulcer, one of enteritis. The average survival time was about two weeks longer than that of the control dogs. It is to be noted that Strikingly, the survival time of the four dogs dying with ulcer is 175 days. This is twice the survival time of the control group. The record of dog 11 is especially striking. Dog 7 may be one of the rare dogs, which after this operation, never develops an ulcer. Yet we diagnosed clinically an ulcer in this dog, before raw pancreas was given.

TABLE VIII

Summary of Data on Prophylactic Therapy

Group Procedure	No. Dogs	Developed Ulcer	Did Not Develop Ulcer	Time of Death with Ulcer	Time of Diagnosis of Ulcer	Time of Death Without Ulcer	Incidence ulcer %	Calculated Prophylactic Value Curve A	Curve C	Av. Survival Time
A Control Group	42	42	0	Min. 2 wks. Max. 17 wks. Av. 78 days	Min. 3 wks. Max. 14 wks. Av. 52 da.		100			7- da
B Mucin Group t.i.d. and b.i.d.	16	6	10	Min. 7 wks. Max. 18 wks. Av. 82 da.	Min. 5 wks. Max. 16 wks. Av. 60 da.	Min. 7 wks. Max. 52 wks.* Av. 131 da.	37	35	53	131 da.*
C Alkali Group b.i.c.	6	5	1	Min. 7 wks Max. 52 wks. Av. 90 da.	Min. 3 wks. Max. 16 wks. Av. 61 da.	49 da.	83			87 da
D Mucin, Alkali, Pancreas Group t.i.d. or b.i.d.	15	5	13 2 dogs no ulcer at 3 yr. 9 mo.	Min. 10 wks. Max. 84 wks. Av. 175 da	Min. 7 wks. Max. Av.	Min. 7 wks. Max. 52 wks. Av. 2 dogs alive, 3 yr. 9 mo.	33	57	70	152+ da.++

*Two dogs did not develop ulcer until mucin therapy was removed.
++ Dog 7 and 11 in this group were assigned only 52 weeks for averaging; whereas they are still alive at 3 yr. and 9 mo., both now without ulcer

one of the dogs survived longer than the maximum control time. More dogs were not used in this series because it has been reported that the administration of alkalies does not prevent the development of ulcers in Mann-Williamson dogs by Meyer and Rubin (9), and by Doctor Mann (personal communication). The attempt to maintain complete neutralization is practically impossible in the dog. These results when viewed in the light of the preceding data strongly indicate that mucin does not act to prevent ulcer primarily through its capacity to buffer free acid.

GASTRIC MUCIN—ALKALI—RAW GROUND PANCREAS

Since the authors were interested chiefly in discovering some way to prevent the development of ulcer in dogs operated by the Mann-Williamson method and in keeping such dogs in good nutritional condition, and since gastric mucin will not prevent ulcer from occurring in all such dogs, regardless of the amount of mucin given twice or three times daily, it was decided to add other possible therapeutic procedures to the mucin regime.

A group of nineteen dogs (Table VII) was operated and placed on the regular diet, including 30 grams of gastric mucin, one gram each of sodium bicarbonate and calcium carbonate thrice daily and 200 grams of raw ground pancreas twice daily. The alkali was given to combat the acidosis and for its neutralizing value. Sodium bicarbonate was used regardless of the fact that it tends to stimulate acid production in the dog (11). Raw pancreas was added to improve digestion, if possible.

That the raw ground pancreas improved the nutrition of some of these animals was not discovered until after the first nine dogs had been operated for some time. So the first nine dogs in Table VII did not receive raw pancreas until some time (1-2 months) after they were operated. Four of the nineteen dogs were discarded because they died of pneumonia at 3 and 4 weeks post-operatively. Of the fifteen animals, ulcer developed in only five, or 33 per cent. The average survival period for the fifteen dogs is very high because two of the dogs are still alive at over three years.

When the data in Table VII are treated by using Curve A in Figure 1, the result obtained indicates that the prophylactic value of the mucin-alkali-raw pancreas regime is 57 per cent and not 66 per cent as indicated by a superficial study of Table VII; using Curve B, the prophylactic value is 70%. These figures are too high because dogs 2, 3 and 12 developed ulcer and according to the curves receive a prophylactic value of 100 per cent, which is due to the fact that they survived longer than the maximum time of the controls without having ulcer by clinical and post-mortem diagnosis.

By comparing the data obtained from the mucin group (Table V) with the data from the mucin-alkali-raw pancreas group (Table VII), one is forced to conclude that the latter therapy is more effective. In this connection it should be realized that the mathematical treatment is not perfect and is only very roughly approximate. In order to arrive at more accurate results, more animals must be used in each group. However, it should be appreciated that experiments of this nature are subject to *very rigorous control*, are expensive and the animals require a large amount of attention, and the inclusion of a larger

TABLE IX

Analysis of Results on Dogs. Surviving 12 weeks or longer, 12 weeks being the time at which 95% of the 42 control dogs had an ulcer

Procedure	No. of Dogs	Ulcer	No Ulcer	Ulcer % Incidence
A. Controls	42	41 developed ulcer prior to 12 weeks	1 developed ulcer after 12 weeks	97
B. Mucin	7	2	5	29
C. Alkali	2	2	0	100
D. Mucin, alkali pancreas	9	4	5 2 still living at 3 yr., 9 mo	44*

*This figure for group D is higher than for group B, because the dogs in group D lived longer. The majority of ulcers occurring in group D were very chronic in type.

number of animals in each group would not be indicated unless the results were less definite than they are.

SUMMARY

It is evident from the results that the administration of gastric mucin, or gastric mucin-alkali and raw pancreas is of prophylactic value in experimental post-operative jejunal ulcer which develops when pancreatic juice and bile are drained into the last few inches of the ileum; but neither therapy is effective in all animals. It can be stated that the addition of raw pancreas to the gastric mucin management is of value in that it improves the nutrition of the animals; but it cannot be stated that the addition of alkali to gastric mucin is of advantage until results have been obtained on a group given gastric mucin and alkalies and on another group given alkalis and raw pancreas (see Tables VIII and IX).

ATTEMPTS TO OBTAIN HEALING OF EXPERIMENTAL JEJUNAL ULCER IN DOGS

Experiments have been performed in an attempt to determine if healing of the jejunal ulcer may be induced by the mucin-alkali-raw pancreas therapy. This problem was not attacked first because it was realized that it would be easier to obtain a prophylactic than a healing effect. This is true because generally by the time these animals develop an ulcer, their nutritional condition is poor and difficult to control.

The experiments were planned as follows: The operation was performed. The animal was then placed on the regular diet with which 100 grams of raw pancreas was

TABLE X

Preliminary Studies on Healing of Ulcer Under Therapy. (In the experiments the ulcer was clinically suspected as being present. Exploratory operation was performed. Photograph of ulcer was taken, if one was present; if not, an artificial ulcer was made)

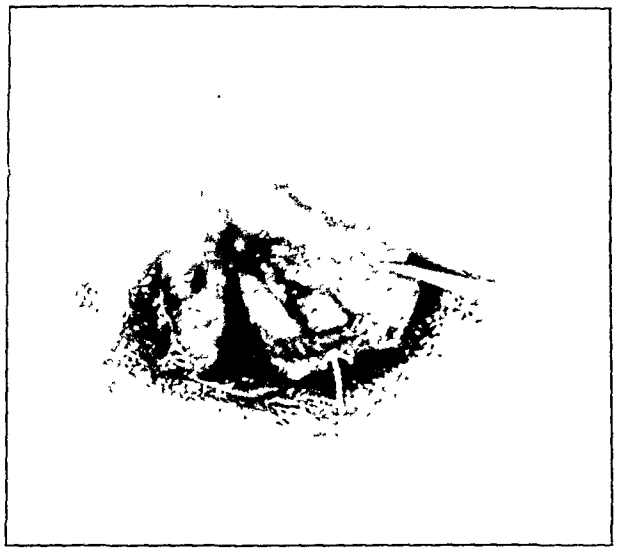
Dog No.	Ulcer found by exploration	% loss of weight between M. W. operation and exploratory	Observations on healing after therapy	Remarks
1	5 weeks. 6x8 mm. involving muscle wall.	30	Ulcer perforated 48 hrs. later.	*This finding caused us to begin therapy on day of operation.* Extension of ulcer probably due to unbuffered post-operative secretion.
2	5.5 weeks. 3 mm. dia. mucosa only involved.	None	Healing in 15 days.	Dog was pregnant. Histological examination showed mucosal defect not completely regenerated.
3	6 weeks. 4x5 mm. muscle layer visible.	17	Healing in 3 wks. Specimen resected by operation. New anastomosis made.	Gained 13% of wt. on therapy in 3 wks. Dog lived 4 months on therapy after resection. Died without ulcer. Histological exam. of resected specimen showed mucosa had covered defect.
4	5 weeks. 2x3 mm. involved mucosa. Linear abrasions of mucosa.	18	Healing in 6 wks. specimen resected new anast. made.	Gained 12% wt. on therapy. Dog lived 16 wks. on therapy after resection. Hist. exam. revealed healing of defect at 16 wks. Dog had chronic indurated ulcer. Was sacrificed. Loss of weight, 25%.
5	6 weeks. No ulcer found. Ulcer 5x4 *made by* excision.	16	42 da. later, ulcer was found to be healed.	Therapy resulted in healing of artificial ulcer. Dog sacrificed. Gained some weight on therapy.
6 W.	6 weeks. 5x3 mm. Muscle layer visible.	20	25 days later ulcer healed.	Distinct scarring of mucosa visible. Regeneration of mucosa incomplete. Dog gained wt. on therapy.
7	7 weeks. 3x5 mm. ulcer.	20	29 da. later spec. ulcer had healed.	Dog died from pneumonia. Dog remained at same wt. on therapy. Histological examination shows defect covered, but regeneration incomplete.
8	3.5 weeks. No ulcer found. 3x5 mm. ulcer made by excision.	25	49 da. later spec. resected. Ulcer had healed.	Could find no ulcer and were uncertain concerning scar in mucosa.

TABLE XI

Observation on Healing of Ulcer by Institution of Therapy (Ulcer Well Advanced as Indicated by Blood Loss)

Observations during the development of ulcer						Results on mucin-alkali-raw pancreas Therapy	
Dog No	Interval between M.-W. operation & diagnosis of ulcer weeks	Loss of weight %	CO_2 Comb. power just prior to ulcer diagnosis	Change in wt. after therapy + gain — loss	Time of survival after diagram of ulcer weeks	Healing of ulcer	Remarks
9	6	25		+5	8	None	Indurated ulcer: died from hemorrhage.
10	8	29		No change	1	None	Perforation.
11	9	31		+5	5	None?	2 ulcers found. One almost healed. Death due to perforation of 2nd perforating type of ulcer.
12	8	35	32.7	—5	3	None	Indurated ucer—hemorrhage.
13*	12	40		+50	56	Complete	After 56 wks. therapy was withdrawn. Dog died in 16 wks. of perforated ulcer. Lost 40% weight.
14	4	20		+15	8	None	Indurated perforated ulcer.
15	4	20		+5	6	None?	Histology showed healing at edges. Hemorrhage from central blood vessel.
16	8	21	42.1	+5	17	None	Indurated perforated ulcer.
17	8	21		—17	6+	None	Indurated ulcer—hemorrhage.
19	9	20		+5	18	None	Indurated perforated ulcer.
20	4	30		—20	3	None	Perforated indurated ulcer.
23	9	11		—21	6	None	Perforated ulcer.
24*	6	33		+55	52	Complete	After 52 wks. therapy was removed. Dog died 50 wks. later of indurated perforated ulcer, loss of weight, 12%.

Dog 18, 21 and 22 died at 9, 6, & 22 died of causes not related to ulcer.



Photograph 1 was made of the ulcer of dog 1, Table 10, at an exploratory operation.

mixed. This mixture was fed three times daily. When the presence of ulcer was diagnosed clinically, the animal was explored, a photograph of the ulcer being made. This was done on eight dogs in this series. On the afternoon



Photograph 2 was made of the ulcer of dog 1, Table 10, 48 hours after the exploratory operation. We believe the marked extension of the ulcer and its perforation was due to the unbuffered gastric secretion which is frequently formed post-operatively after operations on the stomach and upper abdominal viscera.



Photograph 3. This photograph was made at the exploratory operation in dog 2, Table 10. It involved only the mucosa and was found to be healed after 15 days on therapy.

of the same day, mucin was administered by stomach tube, and thereafter *four times a day* in 30 gram doses at 7:00 a. m., 12:00 noon, 5:00 p. m. and 10:00 p.m. The pre-operative diet was instituted again on the second or third day post-operative, the mucin being continued four times a day.

The administration of gastric mucin was started on the same day as the exploratory operation because of the following observation: Dog 1, Table X, was explored on a Saturday morning. A jejunal ulcer, six by eight mm. was found and photographed (Photograph 1) and the animal closed. On Sunday, the animal was given water. Monday morning at 8:00 a. m., the animal died. Autopsy revealed a perforated ulcer with blood in the peritoneal cavity and bowel. On opening the jejunum, it was found that the ulcer had perforated, the perforation measuring six by eight mm., and that the lesion in the mucosa had extended until the ulcer now measured fourteen by twenty-six mm. This marked extension of the ulcer had occurred within forty-eight hours, during which time nothing but water had been allowed. The blood supply had not been disturbed, since the ulcer was on the posterior wall and the exploratory incision was made in the anterior wall. Therefore, we should explain the rapid extension of the ulcer as due to the unbuffered post-anesthetic and operative secretion

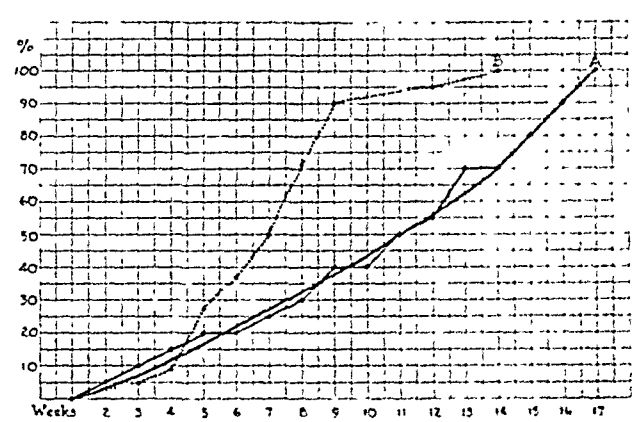


Fig. 1. Curve A represents the percentage survival-time of the 42 untreated control dogs. Curve B represents the percentage diagnosis-time of ulcer in 22 of the dogs; for example, 50% of the dogs had ulcer at 7 weeks.

of gastric juice, which commonly occurs in the dog, acting on a specially susceptible jejunal mucosa.

In Table X are recorded the results of a preliminary study on 8 dogs in which the dogs were explored. Ulcers were diagnosed clinically prior to the exploratory in all dogs but dog 8. One diagnosis was missed, namely, in dog 5. The results show that the healing of two artificially produced ulcers and healing of all spontaneously occurring ulcers was obtained except in one dog.

Encouraged by these results, which bear only on the healing of very early ulcers, we proceeded to study another group in which the ulcer was permitted to progress until the clinical and laboratory evidences of ulcer were much more pronounced. We were certain that the foregoing results applied only to very early lesions, because of the course of some of the animals after the resection operation and particularly because in dog 4 we found that the original ulcer had healed on therapy and a new ulcer 2 cm. distant had appeared. (We have no adequate explanation for the latter observation). Accordingly, observations were made on thirteen dogs. By referring to Table XI, it will be observed that healing of the ulcer was obtained in only two of the thirteen (15%) animals. Although the average survival time after therapy was started is only 14 weeks, it is to be noted that the survival time was extended beyond the maximum control time of 17 weeks in 4, or 30%, (dogs 13, 16, 19 and 24). However, in nine, or 69%, the survival time was extended beyond the eleven week average of the control group.

SUMMARY

This evidence again testifies that the therapy was of value, in that it caused healing in two dogs and delayed lethal hemorrhage and perforation in some but not all of the others. Since these dogs received raw ground pancreas after the Mann-Williamson operation was performed, and developed ulcer in the same time as the controls, it is evident that raw ground pancreas alone has little direct prophylactic value.

LIVER HISTOLOGY

A histologic study of the liver was made in many of these animals because of the occurrence of the spontaneous duodenal ulcer in animals subjected to operative procedures which cause liver damage (10). No changes were found. (Dr. Reymont found no changes in liver function as revealed by ordinary liver function tests).

GENERAL SUMMARY

The prophylactic value of gastric mucin therapy and of gastric mucin-alkali-raw ground pancreas therapy on the post-operative jejunal ulcer (Exalto-Mann-Williamson) that occurs in 95 to 100 per cent of dogs after diversion of the pancreatic juice and bile into the lower ileum has been studied in a relatively large number of animals. We cannot conceive of a more severe test of the therapeutic value of any therapy for "peptic ulcer" than that provided by the "Mann-Williamson preparation." The ulcer which occurs in these animals is believed to be quite analogous to the jejunal ulcer which occurs after gastro-enterostomy in man. The results obtained show that both therapies have a definite prophylactic value, the latter being the more effective. However, it is believed that these therapies are chiefly palliative and do not attack directly the chief etiologic agent of the ulcer studied, which would appear from the results of our gastric analyses, and the studies of others, to be a hypernormal (also continuous) (increase in quantity) secretion of gastric juice, which, because of the diversion of pancreatic juice and bile is not subjected to adequate neutralization in the jejunum, the mucosa of which is susceptible to acid irritation. That a nutritional factor is etiologically concerned cannot be doubted from a careful study of our records, which, however, at the same time, will show that it is not the only etiologic factor concerned. We believe that if one should be able to devise ways to prevent these two factors from operating, the occurrence of ulcer in the Mann-Williamson preparation would be prevented.

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Studies of Pepsin in Human Gastric Juice

III. Physiologic Aspects*,**

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WHEN trying to appraise the condition of any organ, such as liver or kidney, which has many functions, the physician can hardly hope to find a single test which will always be trustworthy and helpful, especially for the detection of slight injuries. Actually he should search with several tests, each designed to probe the functional capacity of some one set of cells in the organ.

Is it not surprising then that we physicians have so long remained content with but one test for gastric function, namely, the titration of hydrochloric acid? We have stuck to this one test in spite of the fact that for years it has been known that there are three main types of secreting cells in the mucous membrane lining the stomach: (1) the parietal cells, which produce little besides hydrochloric acid and water; (2) the chief cells, which produce pepsin and probably other ferments, and (3) the mucoid cells, which produce mucus and perhaps some of the so-called diluting fluid of the stomach.

If the estimation of gastric acidity had been of great and decisive value in the making of diagnoses, one could more easily understand our single-hearted devotion to this one test, and our neglect of other possible tests of gastric function, but actually, in practice, it is rarely of pathognomonic value.

To be sure, a considerable amount of clinical work has been done with pepsin, but unfortunately, the methods used by the earlier workers were crude; usually, the number of cases studies was not sufficient for satisfactory statistical analysis, and seldom was the concentration of pepsin measured in such terms that the results of one investigator could be compared with the results of another.

Because of these defects in the literature on pepsin we shall not attempt to review work already done but shall proceed to a description of our own efforts to gain answers to the many questions that arose in our minds. In beginning this work we wished not only to contribute something to the physiology of gastric secretion but we hoped that estimations of pepsin in human gastric juice might in some cases prove to be of more value to the clinician than the measurements of acidity have been.

Two preliminary papers were published in 1933 (1, 2). We are now able to make a final report on the results of the study of a much larger series of cases. The present paper deals with physiologic considerations, while two others will deal with alterations of pepsin in the presence of disease.

We first had to secure answers to such important basic questions as: What is the best method of securing juice for analyses of pepsin? What is the variability to be expected in repeated tests on one person, and what are the limits of normal secretion? How much does age or sex influence the secretion? To what extent are acid and pepsin secreted together?

The answers given here are based on a study of 5378 analyses of gastric contents; 4255 of these were made on samples removed from men and 1123 on samples removed from women. There were 1381 samples of juice obtained after an Ewald type of test meal, 762 were removed after a night's fast, and 3232 were removed after the injection of histamine.

We do not have as many data from normal persons as we would like, but, fortunately, there are reasons for believing that one can learn much about the variations in the secretion of pepsin in normal persons from a study of patients with gastric or duodenal lesions. Tests have shown that with both pepsin and acid the presence of a lesion may raise or lower the mean, but aside from this shift, the characteristics of the distribution are not affected, and the effects of age and sex are much the same as in normal persons.

TECHNIC

In this paper, for the sake of convenience and brevity, we will speak of test-meal juice, fasting juice, and histamine juice: Test-meal juice was obtained one hour after the ingestion of eight arrowroot cookies and 400 c.c. of water. Fasting juice was obtained in the morning before breakfast. To obtain histamine juice, the drug was injected in doses corresponding to 0.1 mg. for each kilogram of body weight. Beginning ten minutes after the injection, the gastric contents were aspirated as completely as possible every ten minutes until six samples were obtained. A small-bore Sawyer tube was used.

To determine the concentration of free acid, titration was done in the usual way with Töpfer's reagent. Wherever acid is mentioned in this paper the figures represent free acidity.

In measuring the concentration of pepsin we used a modification of the Gates, Gilman and Cowgill method, described by us elsewhere (1). The unit of measurement was established arbitrarily by Gilman and Cowgill as

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representing the proteolytic activity of a 1 per cent solution of a 1:10,000 commercial solution of pepsin.

Test meal juice.—Table I shows the characteristics of test-meal juice as obtained from ninety-six apparently normal men and sixty-three apparently normal women. In 1933 (1), we reported that in most normal men and women, the concentration of pepsin in test-meal juice is less than 500 units, with a mean of 145 units and a median of 135 units. With the data now added, the mean for men is found to be 238 and the median 151 units. For women the corresponding figures were 190 and 110 units. The markedly skewed J-type of percentage distribution can be visualized from Figure 1.

This great skewness or asymmetry of the distributions representing concentration of pepsin is due partly to the fact that the concentration of a ferment varies

Fasting juice.—Table I shows concentrations of pepsin and hydrochloric acid in fasting juice obtained from seventy-seven apparently normal men and fifty-one apparently normal women. It will be seen that the mean acid concentration is lower than that found in test-meal juice, and achlohydria is met with more often. On the other hand, the concentration of pepsin is considerably greater in fasting juice than in test-meal juice. In the case of men, the mean was 371 units, and the median, 190 units. The corresponding figures for women were 256 and 120 units. The range was from 0 to 8500 units.

Histamine juice.—In Table I will be found mean and median values for concentrations of acid and pepsin and volume of juice in the six samples removed at ten-minute intervals after the injection of histamine. It will there be seen that the *concentration* of

TABLE I

Data for normal persons, using three types of juice

	Men							Women						
					Concentration of pepsin							Concentration of pepsin		
	Number of tests	Mean age	Achlorhydria, incidence in per cent	Mean concentration of acid	Mean	Standard deviation	Median	Number of tests	Mean age	Achlorhydria, incidence in per cent	Mean concentration of acid	Mean	Standard deviation	Median
Test-meal juice	96	36	5	44	238	145	151	63	41	3	35	190	133	110
Fasting juice	77	49	29	28	371	344	190	51	46	61	33	256	324	120
Histamine juice 1*	30	48	47	22	578		440	27	45	43	29	602		555
Histamine juice 2*	30	48	20	45	1630		1180	27	45	23	46	826		680
Histamine juice 3*	30	48	20	63	1515		990	27	45	13	57	685		580
Histamine juice 4*	30	48	13	63	1048		800	27	45	13	50	506		305
Histamine juice 5*	30	48	17	64	1137		935	27	45	13	45	536		346
Histamine juice 6*	30	48	10	54	810		505	27	45	13	43	516		346
					Quantity of pepsin**							Quantity of pepsin**		
				Mean quantity of acid**	Mean	Standard deviation	Median				Mean quantity of acid**	Mean	Standard deviation	Median
Histamine juice	30	48	17	42	767	725	340	27	45	22	26	602	790	310

*Figures identify the six samples removed at successive intervals of ten minutes.
**Secreted in the first thirty minutes.

as the square of the amount of substrate digested. However, even when square roots of the values were plotted, the distributions were still somewhat skewed. This may perhaps be explained by assuming, what we have good reasons for believing is true, that our human material is not homogeneous in regard to gastric secretion but consists of at least two groups, one made up of persons with normal concentrations of acid and pepsin and the other made up of persons with abnormally high concentrations. Our impression is that high concentrations are commonly found in a tense type of person whose secretory mechanisms are overly reactive to nervous stimulation. It is conceivable that if, by some anthropologic measurement, we could recognize these two types of persons and segregate data from them, the two distributions representing concentrations of pepsin would be symmetrical.

It will be obvious that, with such skewed distributions, a mean is of little value as an index of central tendency and hence it is that we have depended more on the median or mid-value.

pepsin rose for the first twenty minutes and then fell for thirty minutes to rise again the last ten minutes. The *concentration* of acid and the volume of juice secreted rose together for the first thirty minutes and then fell. These observations agree with those made on animals, all showing that in juice obtained after injection of histamine, the apex of the curve representing concentration of pepsin comes earlier than that representing concentration of acid (Fig. 2).

Since many studies indicate that the acid of the stomach comes from the parietal cells at a constant concentration, which is determined by the osmotic pressure of the blood, the probability is that so long as there is any secreting mucous membrane left in the stomach the concentration of hydrochloric acid will be as nearly normal as dilution by other secretions will permit. Under such circumstances, it would seem that when one wants to get some idea of the extent of injury wrought in the stomach by disease, one should turn to a study of the *quantity* of acid secreted rather than its *concentration*. Similarly, the *quantity* of pepsin secreted in a unit of time might be of more

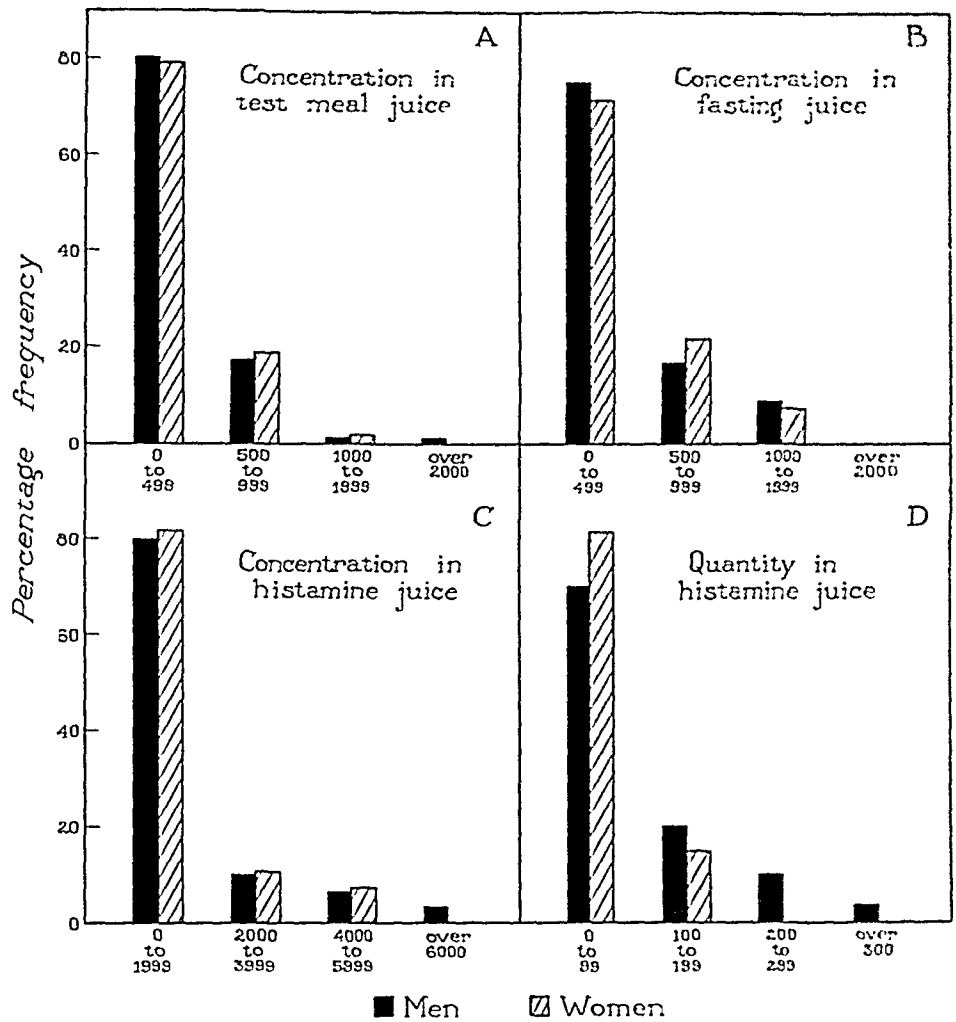


Fig. 1. Percentage frequency distributions showing pepsin values in gastric juice of normal persons. A, Concentration in test-meal juice; B, Concentration in fasting juice; C, Concentration at the peak of the curve of secretion of histamine juice; D, quantity of pepsin secreted in the first thirty minutes after the injection of histamine.

value than the figures for *concentration* in each of the six specimens.

As everyone knows, the quantity of any substance in a given sample of fluid is found by multiplying the figure expressing concentration by the figure expressing volume. Mean quantity of acid and mean quantity of pepsin in each ten-minute sample are shown graphically in Figure 3. The curves representing *quantities* of secretion closely resemble those showing *concentrations*, with the exception that the curve representing quantity of pepsin does not tip up at the end as does that representing concentration of pepsin.

Because, in histamine juice, most of the acid and pepsin is secreted in the first three ten-minute periods, we decided to use as convenient indices to the quantities of acid and pepsin secreted by a given stomach sums of the quantities of acid and pepsin respectively present in the first three samples. From Table I, it will be seen that the mean quantity of acid secreted in the first thirty minutes, expressed in terms of cubic centimeters of tenth-normal hydrochloric acid was 41.7 for men and 26.3 for women, the median value for the corresponding quantity of pepsin secreted in the first thirty minutes, expressed in terms of milligrams of Armour's 1:10,000 pepsin, was 340 for men and 310 for women.

The higher concentrations of pepsin met with in this study were found usually in histamine juice. The mean in normal men varied from 558 to 1610 units in the six ten-minute samples. In women it varied from 496 to 806 units. The corresponding range of the medians was from 420 to 1160 in men and from 285 to 660 in women. In 23 per cent of thirty-one apparently normal men and women we obtained pepsin readings of more than 2000 units in at least one of the six samples. The highest concentration found in apparently normal men and women after the injection of histamine was 4300 units. In 69 per cent of normal men and women the pepsin concentration in histamine juice was more than 500 units, the figure which we have chosen as the upper limit of normal for test-meal juice.

The question arose in our minds as to which would be the best of the six specimens to use if only one estimation of pepsin were to be made. Measurements of pepsin are time-consuming and often it might be desired to make only one such measurement on juice from each patient. From Figure 2, which shows the

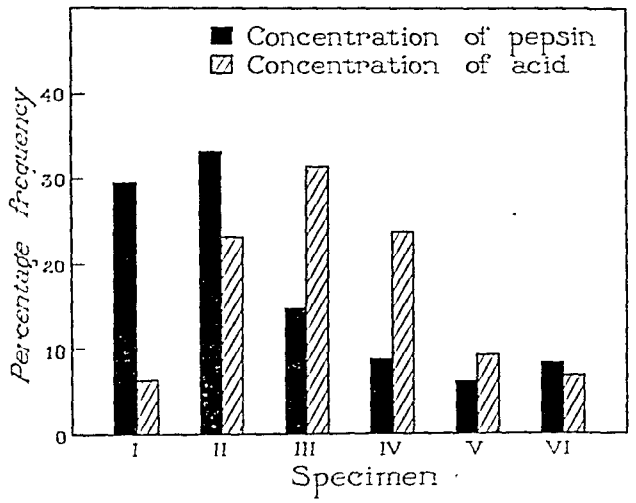


Fig. 2. Percentage frequency distributions of the highest concentration of acid and of pepsin in the six specimens of histimine juice.

frequency of occurrence of the highest concentration of acid and pepsin in the six samples, it appears that it is the second specimen which is the most likely to contain a large amount of pepsin. Still more representative perhaps would be a sample taken after pooling the first two or three specimens.

Another question is, does histamine stimulate the secretion of pepsin? The theory has been advanced that histamine does not stimulate the secretion of pepsin but rather produces a large flow of acid which serves to wash out from the tubules pepsin which has accumulated therein. To test the correctness of this theory, Rivers, Osterberg and Vanzant carried out the following experiment which will be reported in more detail elsewhere. In seventy-one persons they injected a dose of histamine to wash out any pepsin which might be in the tubules, and then, before any more of the ferment could accumulate, they gave another injection of the drug. The curve representing median quantity of pepsin in the second period resembled closely that of the first period. When the curves were superimposed, it could be seen that the only place in which they did not almost coincide was in the parts representing secretion in the first ten minutes, and this divergence was due to the fact that the shape of the curve representing median secretion after the first injection of histamine happened to be unusual. The close similarity of the remainders of the two curves indicated strongly that pepsin was formed continuously in answer to the stimulus exerted by histamine. Also in favor of this view was the fact that the quantity of pepsin secreted following the second injection not only was not lessened, as it would have been if there had been only a washing out process, but it was slightly increased. It seems to be proved then that histamine is a powerful stimulant to the cells which secrete pepsin.

The relations between the pepsin contents of the three types of juice.—The character of the regression lines and the size of the coefficients of correlation showed that there is a high degree of positive correlation between the pepsin readings in the three types of juice obtained at different times from one individual. On the average, the figure expressing concentration of pepsin in test-meal juice was 0.63 of that expressing concentration of pepsin in fasting juice, and 0.35 of that expressing the quantity of pepsin secreted in the first thirty minutes after the injection of histamine. Once we had established this relationship, we were able to combine groups of data based on analyses of the three types of juice by reducing them all to terms of pepsin concentration in test-meal juice. This ability to express with one figure all our observations made with different types of juice was particularly helpful when it came to studying pepsin readings in groups of patients with different diseases.

The best type of juice to use.—After we had studied the characteristics of the three different types of juice, the question naturally arose, should we go on using all three types, or is any one of them so much better than the others, that we should use that and discard the others? In attempting to decide this matter we measured the several types of juice by three criteria: (1) variability in measurements of pepsin when repeated tests are made on the same individual; (2) variability in measurements made on a group of patients with a particular disease, and (3) degree of separation between the distributions representing values of pepsin in normal and diseased persons. Other criteria, such as ease of obtaining the specimen, or comfort and convenience of the patient, were not taken into account.

With all types of juice, the range of the measurements was so great that we felt the need for accumulating large groups of data before attempting to draw conclusions in regard to differences between normal and diseased persons or between patients with different diseases.

On estimating the coefficient of variation (the standard deviation expressed as a percentage of the mean) for repeated measurements of pepsin in gastric secretion taken *from one person*, we found that values

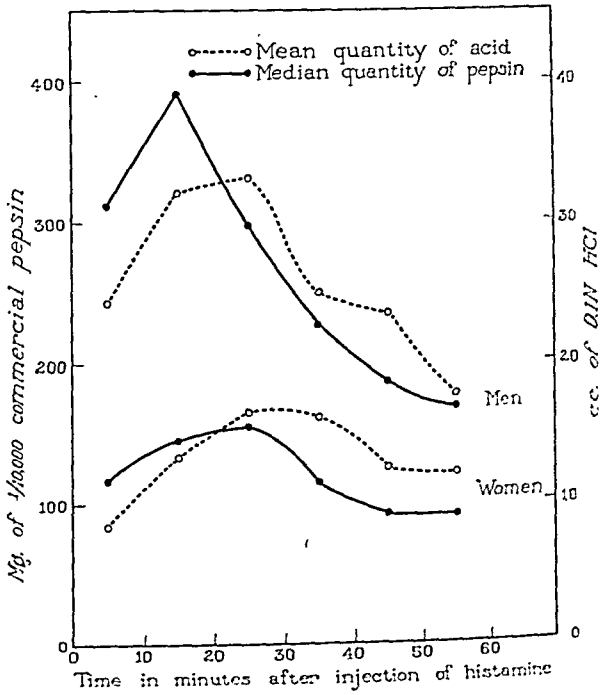


Fig. 3. Curves representing quantities of acid and pepsin secreted in the six specimens of histamine juice. Data were taken from records of normal persons and of persons with gastric and duodenal disease.

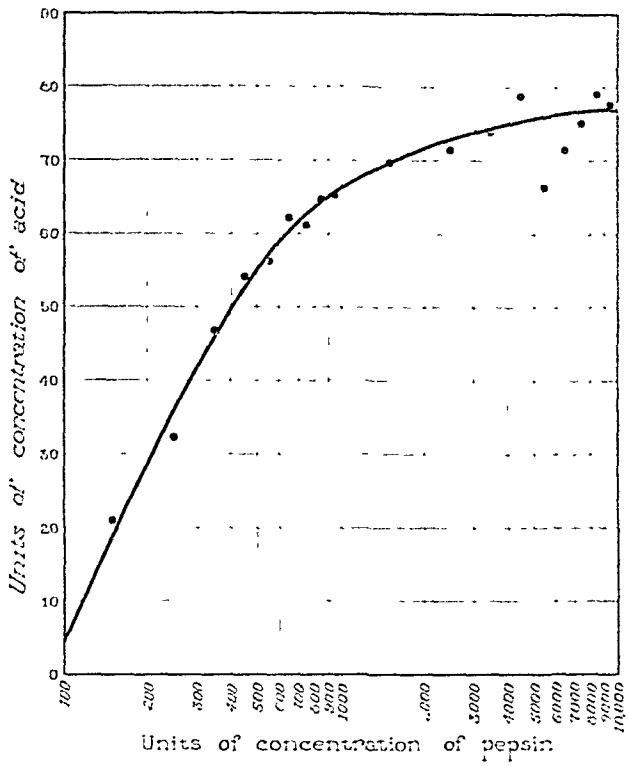


Fig. 4. Regression of mean concentration of acid on concentration of pepsin in 3232 samples of histamine juice obtained from normal men and women, and men and women with diseases of stomach and duodenum. Semilogarithmic paper was used.

from test-meal juice showed the least variability. We obtained from two to nine samples from each of thirty-three persons, and found the coefficient to be 21 per cent. For the corresponding free acid values, it was 13 per cent. The variation in repeated pepsin readings made on fasting and histamine juice was in each case about 50 per cent greater than in readings made on test-meal juice.

The coefficients of variation for pepsin concentrations in samples of test-meal and fasting juice taken *from many normal men and women* were respectively 63 per cent and 108 per cent. For quantity of pepsin secreted in the first thirty minutes after injecting histamine the coefficient was 111 per cent. The coefficient of variation for free hydrochloric acid was one and a half times greater for values in histamine juice than for values in test-meal juice, and it was three times greater for values in fasting juice than for those in test-meal juice.

When it came to distinguishing between normal persons and persons with gastric or duodenal disease, we were unable to find that pepsin determinations on any one juice were better than those on another.

We conclude, then, that test-meal juice is the best to use routinely for clinical determinations of pepsin because it is better than the others when judged by the first two of the three criteria, and so far as the third criterion goes, test-meal juice is as good or bad as are the other two. It is commonly assumed that analyses of histamine juice must be of more clinical value than analyses of test-meal juice because with the former there is no dilution with the fluid in the test-meal; furthermore, one can measure volume of secretion, and can thereby estimate the quantities of acid and pepsin secreted in a given time. Actually, however, when put to a statistical test, analysis of histamine juice did not prove to be as helpful clinically as were analyses made of test-meal juice.

Correlation between concentrations and quantities of acid and pepsin secreted.—Because acid and pepsin must work together to achieve the digestion of protein, and because often they respond to one and the same stimulus, one would expect usually to find them secreted more or less simultaneously and in parallel concentrations, but because they come from different cells, one would expect to find some conditions under which one would be secreted without the other.

Our studies showed that in histamine juice there was usually a considerable degree of positive correlation between concentrations of acid and pepsin, between concentrations of pepsin and volume of juice secreted, and between concentrations of acid and volume of juice. Because of the nonlinear relation between concentrations of pepsin and acid it would not have been pertinent to calculate the coefficient of correlation, and hence we could only draw the regression line as shown in Figure 4. Semilogarithmic paper was used in order to reduce somewhat the curvature of the line and to condense the space required for the scale of pepsin values. Since the points in this figure represent means of the individual observations which, if plotted, would be scattered widely above and below the regression line, it is obviously impossible to use this line to predict with precision the concentration of acid that should go with a given concentration of pepsin. All one can say is that it is probable that a stomach

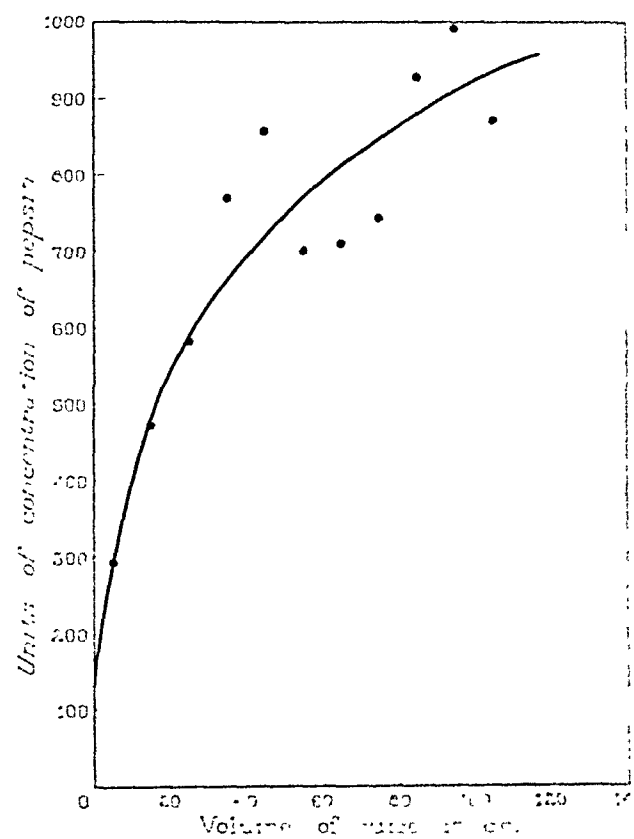


Fig. 5. Regression of median concentration of pepsin on volume of secretion in 3232 ten-minute samples of histamine juice obtained from normal men and women, and men and women with diseases of stomach and duodenum.

which secretes acid in high concentration will also secrete pepsin in high concentration.

When we studied the correlation between concentrations of acid and pepsin in test-meal and fasting juice we obtained the same type of curved regression line observed in the case of histamine juice.

Figure 5 shows that in histamine juice there is a positive correlation between concentration of pepsin and volume of secretion.

Because with histamine juice, the relation between concentration of acid and the amount of secretion was linear in character, we could calculate the coefficients of correlation for each of the six successive samples of juice. They were as follows: for specimen 1, +0.411; for specimen 2, +0.449; for specimen 3, +0.335; for specimen 4, +0.326; for specimen 5, +0.395; for specimen 6, +0.254. These values are lower than some that have been published by other workers.

Since the volumes of test-meal and fasting juices are not dependent on the rate of secretion alone but on a number of other variables, it did not seem worth while to study with such juices the relationships of volume of the gastric contents to concentrations of pepsin and acid.

Striking evidence of the occasional independence of the activities of the parietal and the chief cells was found in the fact that high concentrations of pepsin were observed at times in juice which did not contain any free acid. This apparent independence of the two secretory functions was particularly remarkable when met with during the analysis of histamine juice.

Our reading of the literature led us to believe that we would seldom find much pepsin in juice which did not contain free hydrochloric acid, but actually, we found a number of samples of achlorhydric juice with much more than the normal concentration of pepsin. We cannot say that in these cases the stomach was incapable of secreting hydrochloric acid, but we do know that on a number of occasions when such a stomach was not secreting acid, it secreted pepsin in high concentration. A concentration of pepsin of 3130 units was the maximal one seen in a sample of achlorhydric juice and, strange to say, this specimen was obtained after the injection of histamine, a drug which is supposed to make the parietal cells secrete acid if this is possible. Other values of more than 500 units met with in achlorhydric juice were 530, 535, 540, 580, 680, 790, 980, 1070, 1410, 1450, 1570, 1990, and 3130.

The distribution of figures for concentration of pepsin in achlorhydric juice was skewed just as were the distributions for data from all persons studied. The median was 125 units. In none of the samples of achlorhydric test-meal juice was the concentration of pepsin higher than 300 units. In samples of achlorhydric fasting juice there were 5 per cent with pepsin in concentrations higher than 500 units. With histamine juice there were about 3 per cent of such samples.

We have also seen some samples of juice with a fair concentration of acid and no measurable peptic activity. In two of these cases we had been making daily analyses for two months and hence were able to say that it was an occasional happening which we could not account for in any way (3).

The influence of sex on the secretion of pepsin.—Just as with concentrations of acid secreted, so also with concentrations of pepsin, there is such a marked sexual difference that for statistical purposes, one cannot combine data from men and women. As will have been noticed from the figures presented in this paper, mean and median values for women are usually lower than those for men. Whenever, in the tables, this difference fails to appear, it may be attributed to the fact that we were dealing with a small group of data, some of which were far from the modal value.

The effect of age on the secretion of pepsin.—By combining readings from the three types of juice obtained from persons with duodenal ulcer, we were able to obtain the figures plotted in Figure 6. There it will be seen that the concentration of pepsin falls off with age much as we have found the concentration of acid to do. A similar change in acidity with age seen in normal persons was described in detail in a previous paper (4). It is interesting to note here that Polland (5) has shown that volume of secretion also diminishes with age. The impression gained is that if this loss of power to secrete acid and pepsin, which comes after middle age, is due to a progressive atrophy of the gastric mucosa, then the parietal and chief cells must suffer together.

SUMMARY

A statistical analysis has been made of the concentrations and amounts of pepsin in 6200 samples of gastric juice. Measurements were made with a modification of the Gilman and Cowgill method.

Because of the wide variability in concentrations of pepsin, large groups of data are needed for satisfactory statistical analysis. The median rather than the mean was used as a measure of central tendency because of the marked skewness of the distributions.

Comparative studies were made with test-meal, fasting, and histamine juice.

In test-meal juice, the median for men was 151 units; for women it was 110 units. Five hundred units was taken as the upper limit of normal for both men and women.

In fasting juice, concentrations of pepsin were higher and more variable than in test-meal juice.

In histamine juice the concentrations of pepsin were the highest of all, and the variability was great. In men, the median value ranged in the six samples from 420 to 1160 units; in women it ranged from 285 to 660 units. The curves representing concentration and quantity of pepsin secreted after injecting histamine rose rapidly for twenty minutes and then fell for thirty minutes. The peaks of these curves represent-

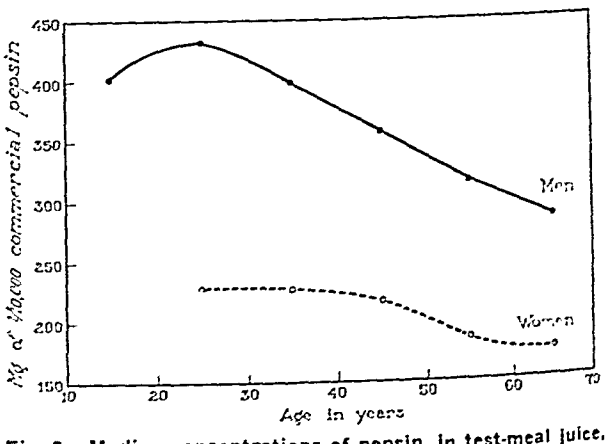


Fig. 6. Median concentrations of pepsin, in test-meal juice, at different ages, in men and women suffering with duodenal ulcer.

ing secretion of pepsin appeared ten minutes earlier than did the peak of the curve representing secretion of acid.

The theory that histamine does not stimulate secretion of pepsin but simply washes it out of the tubules was disproved by comparing curves representing secretion of pepsin in two histamine tests run one immediately following the other.

In studying pepsin in persons with gastric and duodenal disease, test-meal juice was found to be preferable to fasting or histamine juice because in the first named juice the concentration of the ferment was less variable, not only in the individual but in the group.

Because a fairly constant numerical relation was found between figures expressing secretion of pepsin in the three types of juice, it is now possible and often advantageous to convert values obtained with fasting and histamine juice into terms of values for test-meal juice.

There is a considerable degree of positive but nonlinear correlation between the concentrations of acid and pepsin. However, on several occasions, large concentrations of pepsin were found in achlorhydric juice. Occasionally, also, pepsin could not be found in a sample of juice which contained free acid.

There was some degree of positive nonlinear correlation between concentration of pepsin and volume of juice secreted.

The secretion of pepsin was found to decrease with age, much as secretion of acid does. Concentrations of pepsin and amounts of pepsin secreted were decidedly greater in men than in women.

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Permeability to Egg Albumin in Peptic Ulcer*

A Possible Test for Activity of Peptic Ulcers

Preliminary Report

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THE permeability of the gastro-intestinal tract to foreign protein has always been a matter of interesting conjecture. Schloss and Worthen (1) found that when nutritional disorders occurred in children, the digestive tract favored the absorption of foreign protein. Modigliani and Benini (2) observed that casein may be detected in the urine of infants affected with gastro-intestinal disorders by means of anti-casein serum from rabbits. Lust (3) and many others have demonstrated that nutritional disorders in children may permit the passage of undigested protein through the gastro-intestinal tract.

Accordingly, it was decided several years ago to study the permeability of the gastro-intestinal tract of adults to foreign protein. It was observed that when an ulcer existed in the gastric or duodenal mucosa, raw egg white passed through the defect in an unaltered state. A series of eighty-nine patients selected from the wards of the Cook County and Research and Educational Hospitals were fed raw egg white and their urine examined for undigested protein by means of the precipitin test. It was found that in normal individuals and in patients without gastro-intestinal lesions, no precipitin reactions for egg white were present in the blood or in the urine. In individuals with pathology in the gastro-intestinal tract, particularly about the region of the stomach and the duodenum, positive precipitin tests in both blood and urine were demonstrated. In another group of patients, whose lesions were lower down in the bowel, possibly along the terminal ileum or colon, in most cases no permeability to raw egg white was apparent.

A number of patients with active and healed peptic ulcers of the stomach and duodenum were then tested. In this particular series it was shown, with a few exceptions, that the foreign protein was present in the urine and blood of individuals with active peptic ulcers. However, in the majority of cases with healed peptic ulcers no undigested protein passed through the gastro-intestinal tract.

TYPES OF ULCER PATIENTS TESTED

The patients tested in this group may be classified into:

(1) active ulcer group
(2) healed ulcer group

1. The active ulcer group included the three following types:

(a) Individuals presenting subjective symptoms of ulcer with clinical as well as roentgenologic evidence

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(b) Individuals presenting an atypical symptomatology with positive roentgenologic evidence of peptic ulcer.

(c) Patients with long-standing quiescent ulcers with exacerbations of acute symptoms.

2. The healed ulcer group comprised three types:

(a) Perforated peptic ulcers which had been sutured at operation.

(b) Perforated peptic ulcers which had been sealed over with exudate and omentum without operation.

(c) Medically healed ulcers in individuals who are now neither taking powders nor being restricted to a special diet, but who at one time showed positive clinical and roentgenologic evidence of an active ulcer.

TECHNIC OF THE TEST

Rabbits were injected intramuscularly with about 30 c.c. of a 1:10 dilution of egg white fixed in aluminum cream according to the method of Hektoen and Welker (4). At the end of fourteen days, the serum was tested for its precipitin titre for egg white. If the antiserum exhibited a titre of 1:100,000 or more, the animal was bled to death and the serum preserved in tightly corked vials, into which a few drops of redistilled chloroform were placed to prevent mold formation. If the titre of 1:100,000 was not reached, the rabbits were allowed to live for another ten to fourteen days and were again tested. Occasionally, further injections of egg white were given until a serum of sufficient strength was obtained. No serum was used unless it had a titre of 1:100,000 or more.

The whites of two raw eggs, stirred into a little water, were then fed to individuals, with and without digestive tract pathology. The egg white was given at 11 a. m., about three hours after breakfast, and the patients instructed not to eat anything until 1 p. m. Individual voidings of urine on the first day were taken at 12 noon, 3 p. m., 6 p. m., and 9 p. m. Twenty-four hour specimens from 7 a. m. to 7 a. m. were taken on the second day and likewise on the third day. In the last group of about fifty patients, the raw egg white was fed at 11 a. m.; and only one twenty-four hour specimen from 11 a. m. to 11 a. m. was collected.

A higher titre of antiserum can be obtained by using crystallized egg albumin as the antigen instead of raw egg white. The titre obtained in the antisera prepared with crystallized egg albumin ranged between 1:500,000 and 1:1,000,000. It was this antiserum which was used in the last fifty cases. The method of preparation of the anti-egg albumin serum was exactly the same as in the case of the egg white serum. The crystallized egg albumin was prepared according to the method of Cole (5).

In the first forty patients, the urine was tested undiluted and in dilutions of 1:10, 1:100, and 1:1000 with normal saline. In the last fifty cases, the urine was tested either undiluted, or diluted 1:10 with normal saline. Occasionally, where the precipitating serum and the undiluted urine mixed without layer formation, the urine was diluted 1:2 and tested. One-half c.c. of the antiserum was added to each precipitin tube containing one-half c.c. of the undiluted and diluted urine, so that distinct layer formation occurred. The tubes were left undisturbed at room temperature for one hour and the results noted. Control tests were carried out with one-half c.c. of normal rabbit serum in place of the precipitating serum, and also with the addition of one-half c.c. of the antiserum to the normal saline.

A positive test was one that showed a definite white band at the junction of the urine and serum layers. A *questionable result* was one that showed no white band formation, but a white precipitate in the upper portion of the urine in the precipitin tube.

In order to prove that the undigested protein was present in the blood stream, in the first six patients with active ulcers, blood samples were drawn on the first day at 2 and 4 p. m. (along with urine voidings at 12 noon, 3, 6, and 9 p. m.). In both blood and urine, the precipitin reaction was positive for egg albumin. It had been observed by Schloss and Worthen (1), Ascoli (7), Lust (3), and others that the foreign protein appears in the blood stream earlier and for a shorter period of time; while in the urine it appears later but persists longer. The testing of blood for the undigested protein was then abandoned, as this would have necessitated frequent withdrawals of blood specimens, a matter of great inconvenience to most patients.

DISCUSSION OF RESULTS

In Table I may be seen a series of twenty-nine cases without peptic ulcer pathology. Twenty-two of these gave a negative precipitin reaction. Two gave a doubtful result and five were definitely positive. The five patients whose urine showed a positive reaction were diagnosed tentatively as having dietary diarrhea (2 cases), spastic colitis, drastic catharsis, and tapeworm infestation. The two cases of dietary diarrhea and those of spastic colitis and tape worm infestation all gave a positive chemical test for blood in the stools (four plus in the cases of spastic colitis and tape worm infestation). No roentgenographic studies of the gastro-intestinal tract had been made at the time of the testing of the five patients. The positive precipitin reaction in the case of the patient who had been given drastic cathartics (A.S.) cannot be explained unless some overlooked gastro-intestinal pathology was present. In the four other positive patients, it is fairly certain that a defect of the mucosa of the digestive tract exists, the site of which cannot be definitely located.

TABLE I

Patients Without Peptic Ulcer Pathology

Name	Hospital	Diagnosis	Precipitin Reaction
R. S.	R. E. H.	Arthritis Deformans	—
M. T.	R. E. H.	Congenital Heart Disease	—
E. M.	R. E. H.	Hysterical vomiting	—
F. G.	C. C. H.	Portal Cirrhosis	—
G. N.	C. C. H.	Acute Cholecystitis	—
H. J.	C. C. H.	Cholelithiasis	—
J. K.	C. C. H.	Toxic Hepatitis (with non-visualization of gall bladder)	—
E. L.	R. E. H.	Ulcerative Colitis	—
W. K.	C. C. H.	Ulcerative Colitis	—
S. M.	C. C. H.	Ulcerative Colitis	—
R. S.	C. C. H.	Ulcerative Colitis	—
D. H.	C. C. H.	Amoebic Dysentery	—
L. B.	C. C. H.	Spastic Colitis	—
R. K.	C. C. H.	Spastic Colitis	—
W. S.	C. C. H.	Non-specific Enteritis	—
J. L.	C. C. H.	Diarrhea—etiology unknown	—
M. H.	C. C. H.	Diarrhea with multiple Fistulae-in-Ano	—
J. W.	C. C. H.	Secondary Anemia and suspect Peptic Ulcer	—
R. W.	C. C. H.	Suspect Carcinoma of Stomach	—
T. H.	C. C. H.	Carcinoma of Stomach	—
J. L.	R. E. H.	Drastic Catharsis	—
T. R.	R. E. H.	Drastic Catharsis	—
H. W.	C. C. H.	Bleeding Carcinoma of Esophagus	±
W. K.	C. C. H.	Ulcerative Colitis. (Same patient as above given egg white enema three days later)	±
A. S.	R. E. H.	Drastic Catharsis	±
J. J.	C. C. H.	Dietary Diarrhea	—
R. L.	C. C. H.	Dietary Diarrhea	—
J. O.	C. C. H.	Spastic Colitis (4 plus blood in stools)	+
G. G.	C. C. H.	Tapeworm with atypical ulcer history (4 plus blood in stools)	+

The two cases which gave a doubtful reaction were those of a patient with a bleeding carcinoma of the esophagus and one who had ulcerative colitis. The latter patient was given a two quart tap water enema into which had been stirred the whites of two raw eggs. The enema was expelled almost as soon as given. (Two days before this patient had received the egg white by mouth. No absorption of the foreign protein was observed).

Four cases of liver and gall bladder disease showed no permeability of the gastro-intestinal tract to foreign protein. The test may prove to be of some value in facilitating a possible differentiation between gall bladder and gastric disease.

In one case, that of carcinoma of the stomach, the patient (T.H.) had been previously diagnosed as having a gastric ulcer. On testing him with egg white a negative precipitin reaction was obtained. When the patient was operated upon, one week later, he was found to have an ulcerative, indurated carcinomatous lesion of the pars media.

DISCUSSION OF RESULTS

Table II refers to a group of forty-two patients having active peptic ulcers. All except thirteen showed evidence of the absorption of foreign protein. Six of the patients (those marked with an asterisk on the Table) had completed a course of treatment with intramuscular injections of an aqueous solution of histidine.

TABLE II

Patients With Active Peptic Ulcers

Name	Hospital	Diagnosis	Precipitin Reaction
R. S.	C. C. H.	Bleeding Duodenal Ulcer	+
D. C.	C. C. H.	Bleeding Duodenal Ulcer	+
M. F.	C. C. H.	Bleeding Duodenal Ulcer	+
C. L.	C. C. H.	Bleeding Duodenal Ulcer	+
H. P.	C. C. H.	Bleeding Duodenal Ulcer	+
U. M.	C. C. H.	Bleeding Duodenal Ulcer	+
G. O.	C. C. H.	Bleeding Duodenal Ulcer	+
*D. V.	C. C. H.	Bleeding Duodenal Ulcer	+
L. G.	C. C. H.	Bleeding Duodenal Ulcer	+
K. B	C. C. H.	Bleeding Duodenal Ulcer	+
A. L.	C. C. H.	Bleeding Duodenal Ulcer	+
J. D.	C. C. H.	Bleeding Duodenal Ulcer	+
C. L.	C. C. H.	Bleeding Duodenal Ulcer (Patient gave + test one year ago also)	+
A. B.	C. C. H.	Penetrating Duodenal Ulcer	+
A. R.	C. C. H.	Duodenal Ulcer	-
I. B.	C. C. H.	Duodenal Ulcer	+
E. W.	C. C. H.	Duodenal Ulcer	+
H. W.	C. C. H.	Duodenal Ulcer	+
T. G.	C. C. H.	Chronic Duodenal Ulcer	+
T. M.	C. C. H.	Duodenal Ulcer	+
*J. W.	C. C. H.	Duodenal Ulcer	+
*C. D.	C. C. H.	Duodenal Ulcer	+
*V. R.	C. C. H.	Duodenal Ulcer	+
*J. B.	C. C. H.	Duodenal Ulcer	+
M. K.	C. C. H.	Duodenal Ulcer	+
A. S.	C. C. H.	Hour-glass constriction due to gastric ulcer	+
T. T.	C. C. H.	Gastric Ulcer with 100% retention	+
S. A.	C. C. H.	Gastric Ulcer with Obstruction	+
V. M.	C. C. H.	Penetrating Gastric Ulcer	±
*A. W.	C. C. H.	Suspect Duodenal Ulcer	±
R. J.	C. C. H.	Duodenal Ulcer	±
H. W.	C. C. H.	Suspect Bleeding Duodenal Ulcer	-
T. B.	C. C. H.	Bleeding Duodenal Ulcer	-
G. M.	C. C. H.	Bleeding Duodenal Ulcer	-
O. T.	C. C. H.	Duodenal Ulcer	-
J. K.	C. C. H.	Duodenal Ulcer	-
W. L.	C. C. H.	Duodenal Ulcer	-
A. K.	C. C. H.	Duodenal Ulcer	-
J. F.	C. C. H.	Duodenal Ulcer	-
C. G.	C. C. H.	Duodenal Ulcer	-
H. B.	C. C. H.	Gastric Ulcer	-

TABLE III

Patients With Healed Peptic Ulcers

Name	Hospital	Diagnosis	Precipitin Reaction
J. P.	C. C. H.	Gastro-enterostomy following Duodenal Ulcer, Sept., 1932	+
J. C.	C. C. H.	Gastro-enterostomy following Duodenal Ulcer, April 1932	+
J. W.	C. C. H.	Gastro-enterostomy following Duodenal Ulcer, March 1934	+
H. C.	C. C. H.	Perforated Peptic Ulcer, Feb. 1934	-
A. A.	C. C. H.	Perforated Peptic Ulcer, Jan. 1934	-
J. D.	C. C. H.	Perforated Peptic Ulcer, Oct. 1933	+
E. L.	C. C. H.	Perforated Peptic Ulcer, Nov. 1933	+
R. W.	C. C. H.	Perforated Peptic Ulcer, March 1934	-
F. W.	C. C. H.	Perforated Peptic Ulcer, without operation, Aug., 1933	-
O. F.	C. C. H.	Perforated Peptic Ulcer, Feb. 1934	+
V. P.	C. C. H.	Perforated Peptic Ulcer, March, 1934	+
E. M.	Mt. Sinai	Bleeding Ulcer (symptom-free for 10 years with no dietary restrictions)	+
A. B.	C. C. H.	Duodenal Ulcer (6 months without symptoms — no dietary restrictions)	-
O. L.	C. C. H.	Duodenal Ulcer (1 year without symptoms — no dietary restrictions)	+
*J. G.	C. C. H.	Gastric Ulcer of long duration treated with Histidine—no treatment for 3 months at time of testing	+
L. L.	C. C. H.	Penetrating Gastric Ulcer on modified Sippy management for several months in ward	+
R. S.	C. C. H.	Duodenal Ulcer for 1½ years—some symptoms—dietary restrictions	+
A. F.	C. C. H.	Duodenal Ulcer—6 months—some symptoms—dietary restrictions	+

In all the cases of bleeding peptic ulcer, the precipitin reaction was striking. It seems in these cases that when the chemical test for blood on the feces is strongly positive, the precipitin reaction on the urine also is strikingly positive, as manifested by a heavier white band at the junction of the urine and antiserum. A fair conception then of the size and extent of the pathologic process may be had from the amount of precipitate which forms between the urine and the antiserum.

One patient (C.L.) who now is positive also showed a positive precipitin reaction one year ago.

Another case (A.B.), who gave a positive result at one time, became negative six months later after being placed upon proper dietary regime.

Of the three patients who gave "doubtful" evidence of permeability to foreign protein, one (A.W.) had received a course of histidine injections. Another patient (V.M.) showed positive roentgenologic evidence of a small penetrating ulcer on the lesser curvature of the pars media. On three occasions her stools have given a negative chemical test for blood. There is no explanation for the "doubtful" result in the third case (R.J.).

Two of the ten patients (H.W. and H.B.), who gave negative precipitin reactions, should really have been placed into the healed ulcer group. One (H.W.) came to operation where it was found he had a mass of dense adhesions binding down the stomach and duodenum to

the surrounding structures, the result, the surgeon thought, of an old healed "forme fruste" ulcer. The other patient who gave a negative result (H.B.) has been a ward worker in the hospital for the past three years and may have become healed in the course of his stay.

The results of the remaining eight ulcer patients who showed no undigested protein in the urine cannot be explained unless the test was at fault or the roentgenologic evidence insufficient. In the majority of the patients in this group the history and clinical findings were atypical. Stool examinations for blood were negative in most of these cases.

DISCUSSION OF RESULTS

The last series of cases deals with a group of eighteen healed peptic ulcers (Table III). The three gastro-enterostomized patients in this group gave a negative precipitin test. Of the eight perforated duodenal ulcer cases, seven were operated upon and one healed on Ochsner's therapy without operative interference. Six of these showed no precipitin reactions for egg white in the urine. The two patients, whose gastro-intestinal tracts were permeable to undigested protein, both complained of slight pain after eating at the time their urine was tested. The two patients on dietary management, who showed positive precipitin reactions in the urine, have both complained of symptoms within the last month.

COMMENT

It may be possible to show the presence of a healthy or pathological gastro-duodenal mucosa by the simple test of feeding raw egg white to patients and testing for egg white protein in their urine by means of the precipitin test. It would appear that this test can be utilized to determine whether a peptic ulcer is active or quiescent. The test may possibly be of use in differentiating between gall bladder and gastric disease. It is not believed that the test is specific for duodenal or gastric ulcer alone, but that other ulcerative conditions of the gastro-intestinal tract may give a positive precipitin reaction.

Further investigations will soon be carried out on more cases of gall bladder and peptic ulcer disease. Ulcerative conditions of the lower bowel will be studied, not only by means of oral ingestion of raw egg white, but also by means of retention egg white enemas. (A possible explanation of the failure to demonstrate precipitin reactions in cases of ulcerative lesions of the colon and terminal ileum is that the protein fed by mouth becomes broken down by digestion and bacterial decomposition long before the ulcerative defects of the mucosa are reached).

Considering the circumstances under which this work had to be carried on, there is a possibility that some of the false positive precipitin reactions may have been true reactions and that the diagnosis was erroneous. Some of the false negative reactions may be attributed to partial healing of the ulcer.

CONCLUSIONS

1. It seems that individuals without gross lesions in the mucosa of the upper portions of the alimentary tract do not give the egg white precipitin test in the urine, excepting in 20% of cases that might possibly be considered as having given a false positive result.
2. Patients with active peptic ulcers whether located in the stomach or duodenum have yielded the precipitin reaction in 75% of the cases. This might be considered to introduce a possibility of a 25% false negative reaction.
3. Patients with healed peptic ulcer gave a negative reaction in all but 20% of the cases studied.
4. In spite of the possibility of false positive and false negative reactions in a certain percentage of cases, it seems that the test may be of value as corroborative evidence of the probable presence, or absence, of active peptic ulcer, or other mucous membrane lesions, in the upper portion of the digestive tube, and in differentiation from gall bladder and other diseases producing similar clinical pictures.

I wish to thank Dr. William H. Welker for his kind help in directing this problem. I also wish to thank Dr. Harry A. Singer and his associates for the clinical case material they have furnished.

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SECTION III—*Nutrition*

The Influence of Fruit Ingestion Before Meals Upon the Bacterial Flora of Stomach and Large Intestine and on Food Allergins*

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THE influence of various fruits upon gastro-intestinal function has been studied in this laboratory for the past few years. The intra-alimentary contents, from the oral cavity to the anal opening, depend upon the materials ingested, the fluids secreted, and the bacterial flora in the lumen of this tract. We have been particularly interested in the bacterial flora and the acid-base equilibrium of the contents of the gastro-intestinal tract. There are definite communities of bacterial life residing within the lumen of the alimentary canal. The flora of the various zones or levels are distinct and characteristic, although the lumen and mucosa are continuous.

Arnold, Ryan and Korando (1), Arnold (2) reported studies on fruit and vegetable feedings in rodents in relation to bacterial flora, acid-base equilibrium and susceptibility to orally ingested pathogenic bacteria. It was decided to extend these observations to include some human subjects. In the course of this work certain fruits were fed to fasting persons and the gastric response to such a fruit meal followed by the usual methods of aspirating samples at short time intervals. The bactericidal power of the gastric contents was determined during the course of these studies. Hanszen (3) reported these observations in a preliminary paper.

During the course of the above mentioned experiments we became interested in the problem of ingesting a small amount of some fruit an hour or so before a regular meal. We began these studies in this manner because we wished to determine the gastric pattern of reaction to the fruit alone. It was necessary to study the influence of a fruit premeal on the utilization of food ingested at the subsequent meal before such a dietetic procedure could be recommended. We wished to study in greater detail the passage of viable bacteria from the stomach to the large intestine. The factors influencing the length of sojourn of orally ingested bacteria in the large intestine was another part of our problem.

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THE INFLUENCE OF A PREMEAL ON THE PASSAGE OF ORALLY INGESTED BACTERIA TO THE LARGE INTESTINE

Five subjects were used for the first part of these experiments. There were seventy-five test meals carried out with high enemas for recovery of ingested bacteria. A Rehfus tube was used for aspirating gastric contents. All subjects were young adults with normal gastric patterns. The gastric contents after each premeal, and just before the ingestion of the test meal containing B. prodigiosus was aspirated. The hydrogen-ion concentration was more acid than pH. 3.0 in each instance; that is, each subject had free acid at the time the subsequent meal was ingested. Only one protocol will be given as an example of this experiment. Table I shows the results of fourteen experiments carried out on a young male age twenty-seven. The type of premeal, the subsequent bacterial test meal, the time elapsing between the two and the total number of viable B. prodigiosus ingested, the total number recovered in a viable state from the colon washings with the per cent recovered are indicated in this table.

The next series of experiments were to test the influence of bananas, oranges and apples when eaten one hour before a meal, upon the passage of living bacteria through the stomach to the large intestine. The fruit was ingested after twelve hours' fasting, and one hour later 200 c.c. of fresh whole pasteurized milk containing a known number of B. prodigiosus. Several hundred very small colored paraffin beads were added to serve as markers for subsequent colon washings. These wax beads float on top of the aqueous suspensions of fecal material. Different colored paraffin beads allow excellent segmentation of large intestinal contents in relation to time of food ingestion. No food or water was consumed before the next regular meal, which was four hours after the B. prodigiosus and milk was ingested. Different colored paraffin beads were used as markers for this meal. Eight hours after

TABLE I

Influence of premeal upon passage of viable bacteria to large intestine

Pre Meal	Test Meal	Interval between meals	B. prodigiosus in million		Percent B. prodigiosus recovered
			Ingested	In colon washings	
None	200 c.c. tap water and B. prodigiosus		1168.00	156.00	13.00%
1 glass water	1 glass milk and B. prodigiosus plus sweet roll, bacon, egg, toast, 1 glass water	1 hour	1808.00	507.00	28.00%
None	200 c.c. tap water and juice of one lemon plus B. prodigiosus, pH 2.8		1420.00	6.48	0.40%
None	150 c.c. tap water and juice of one lemon plus B. prodigiosus, pH 2.6		980.00	0.00	0.00%
200 c.c. sweet milk	200 c.c. tap water and B. prodigiosus	1 hour	1050.00	0.00	0.00%
1 pint whole sweet milk	200 c.c. tap water and B. prodigiosus	1¾ hours	2200.00	14.40	0.65%
Two medium sized bananas	200 c.c. sweet milk plus B. prodigiosus	1½ hours	1816.00	4.80	0.26%
60 grams banana powder in glass of water	200 c.c. sweet milk plus B. prodigiosus	1½ hours	5088.00	0.00	0.00%
60 grams banana powder and 200 c.c. 2% citric acid	200 c.c. sweet milk plus B. prodigiosus	1½ hours	3520.00	12.00	0.34%
60 grams banana powder in glass of water	200 c.c. sweet milk plus B. prodigiosus	2 hours	3200.00	1.40	0.04%
1 whole grapefruit pH 3.0	200 c.c. sweet milk plus B. prodigiosus	10 min.	1800.00	50.40	2.80%
1 whole grapefruit pH 3.0	200 c.c. sweet milk plus B. prodigiosus	30 min.	2040.00	0.00	0.00%
140 c.c. grapefruit juice pH 3.0	140 c.c. sweet milk and B. prodigiosus	22 min.	800.00	0.00	0.00%
250 c.c. canned tomato juice	200 c.c. sweet milk plus B. prodigiosus	30 min.	1600.00	4.80	0.30%

the milk and test bacteria were consumed, a high enema was given, two successive washings each with 1500 c.c. of sterile water. The B. prodigiosus was counted in the usual manner by dilutions and culture on representative samples of well mixed washings. Four healthy young men, ages nineteen to twenty-eight with normal gastric secretory and motor functions were used for these experiments. Table II gives

TABLE II

The relative efficiency of fresh banana, orange and apple when used as a premeal and control without premeal. Subjects fasted twelve hours before fruit premeal. Two hundred c.c. of whole cow's milk inoculated with B. prodigiosus were drunk one hour after fruit premeal

Subject	Premeal	Millions of B. prodigiosus ingested	Percentage of B. prodigiosus recovered from colon 8 hours after ingestion
A. H.	None	420.00	87.00%
E. H.	None	420.00	43.00%
W. B.	None	420.00	94.00%
F. B.	None	420.00	60.00%
A. H.	Pulp of one banana = 80 grams	987.00	0.127%
E. H.		987.00	0.134%
W. B.		987.00	0.372%
F. B.		987.00	0.083%
A. H.	Pulp and juice of one orange = 94 grams	576.00	4.237%
E. H.		576.00	1.940%
W. B.		576.00	5.320%
F. B.		576.00	7.220%
A. H.	Pulp of one apple = 104 grams	1108.00	12.405%
E. H.		1108.00	20.480%
W. B.		1108.00	5.375%
F. B.		1108.00	9.505%

the results obtained using fresh banana, orange and apple. The number of viable B. prodigiosus ingested with the milk and the percentage recovered from the enema fluid are indicated. The first results shown in this table are controls with 200 c.c. plain milk plus the test dose of B. prodigiosus without a fruit premeal to show the passage of these bacteria through the stomach and small intestine down to the lower levels of the large intestine in a viable state.

Dessicated banana and oranges were used for premeals in the same way, using the same technic as for the fresh fruit. These dried fruit samples were in the form of flasks or films, supplied by the courtesy of the Sardik Laboratories, New York City. Table III gives the results of these experiments.

SUMMARY

The gastro-duodenal bactericidal mechanism is most effective in preventing viable bacteria reaching the large intestine when the gastric contents contain free acid, or when the material within the lumen is completely saturated with acid. A small premeal aids in creating this type of intra-gastric environment.

Many of the test bacteria administered with fresh whole cow's milk (200 c.c.) can be recovered in a viable state from the large intestine eight hours after ingestion. One banana eaten one hour before the milk is ingested reduces the number of viable test bacteria recovered to less than one-half of one per cent. We found banana more effective as a premeal than orange and apple in this respect. Dried apple and banana in the same quantities exercised similar influences in the destruction of orally ingested bacteria under the conditions of our experiments.

TABLE III

The influnce of dessicated apple and banana on passage of test bacteria through the alimentary tract. Subjects fasted twelve hours before fruit premeal. Two hundred c.c. of whole milk inoculated with B. prodigiosus were ingested one hour later

Subject	Premeal	Millions of B. prodigiosus ingested	Percent of B. prodigiosus recovered from the colon after 8 hrs.
E. H.	40 grams dried banana with 200 c.c. water	740	0.04%
A. H.		740	0.85%
F. H.		740	2.90%
E. H.	40 grams dried apple with 200 c.c. water	430	1.01%
A. H.		430	0.00%
F. B.		430	1.80%
A. H.	70 grams dried banana with 200 c.c. water	335	0.034%
E. H.		335	0.007%
W. B.		335	0.135%
F. B.		335	0.000%
A. H.	70 grams dried apple with 200 c.c. water	520	none
E. H.		520	none
W. B.		520	none
F. B.		520	none

THE INFLUENCE OF FRUIT PREMEAL UPON THE UTILIZATION OF PROTEINS, FATS AND CARBOHYDRATES OF THE SUBSEQUENT MEAL

Pincussen (4) reviewed the literature on the utilization of various food by man. It was necessary to establish the comparative utilization of the proteins, fats and carbohydrates in a meal including a given amount of fruit, then for the same meal with the fruit eaten one hour before. The authors visualize an increasing field of usefulness of the premeal for certain types of gastric functions and for added protection of the alimentary tract against exogenous ingested bacteria. The possibilities of utilizing the premeal for food sensitive individuals will be discussed later in this paper. It was therefore necessary to establish the food utilization of the regular meal after a fruit premeal. The utilization of fats, carbohydrates and proteins introduced into an actively secreting and digesting stomach has not been recorded in literature.

Utilization of proteins: Nine healthy subjects of ages seventeen to fifty-eight years were used in these experiments which involved ninety-two analyses. Three different protein test meals were used. The program of each subject was as follows:

First day:

7-8 A. M. A high enema consisting of two washings of 1500 c.c. each.

9 A. M. Test meal followed immediately by ingestion of two bananas.

1 P. M. Four bananas.

6 P. M. A high enema, two washings of 1500 c.c. each.

Second day: Same as the first day.

Third day:

7-8 A. M. Enema.

9 A. M. Two bananas.

10 A. M. Test meal.

2 P. M. Four bananas.

7 P. M. Enema as on first day.

Fourth day: Same as on third day.

The total quantity of the evening washings was made slightly acid by addition of sulfuric acid to prevent loss of ammonia. One hundred grams of corn starch were then added and the mixture was heated to boiling while being stirred. This yielded a rather thick homogeneous fluid suspension of the particulate matter obtained from the large intestine. Two 100 c.c. samples of the liquid were then analyzed for nitrogen by Kjeldahl's method, and the total nitrogen recovered from the colon nine hours after the test meal had its origin in the bananas ingested and in mucus and bacteria from the intestine as well as in the test meal. However, since these factors were constant throughout all experiments the results are significant since they indicate the relative utilization of the test meal when taken after or with bananas. It is evident from Table IV that protein utilization is practically the same whether the protein is taken on an empty stomach or in one in a state of active digestion.

Utilization of Fat: The program of each subject was the same as that described under Utilization of Protein with the exception that a meal rich in fat was substituted for the protein test meal.

TABLE IV

Protein Utilization: Quantity of nitrogenous material recovered from Colon nine hours after ingestion of the several meals listed below. Each figure represents an average taken from two experiments made on two consecutive days and is the total quantity in grams of nitrogen recovered from the colon

Subject	400 c.c. evaporated milk. Total nitrogen 4.1444 gms.		400 c.c. whole milk. Total nitrogen 2.128 gms.		200 grams lean beef. Total nitrogen 6.132 gms.	
	2 bananas 1 hour before meal	2 bananas with meal	2 bananas hour before meal	2 bananas with meal	2 bananas hour before meal	2 bananas with meal
1	0.560 gms.	0.786 gms.	0.595 gms.	0.480 gms.	0.520 gms.	0.590 gms.
2	0.726 gms.	0.498 gms.	0.520 gms.	0.640 gms.	0.750 gms.	0.845 gms.
3	0.585 gms.	0.690 gms.	0.574 gms.	0.515 gms.		0.625 gms.
4	0.427 gms.	0.535 gms.	0.394 gms.	0.558 gms.	0.726 gms.	0.690 gms.
5	0.640 gms.	0.770 gms.		0.550 gms.	0.824 gms.	0.855 gms.
6	0.432 gms.	0.620 gms.	0.570 gms.	0.728 gms.	0.435 gms.	0.685 gms.
7	0.550 gms.	0.495 gms.				
8					0.843 gms.	0.755 gms.
9					0.740 gms.	0.856 gms.
Average	0.560 gms.	0.627 gms.	0.530 gms.	0.573 gms.	0.691 gms.	0.737 gms.

Colon washings were acidified with HCl to convert fatty salts to fatty acids, and the latter together with neutral fats were extracted by ether. The ether and volatile fatty acids were then driven off by heating in an evaporating dish, leaving only solid fat which was weighed. The volatile fatty acids were eliminated because their origin was most probably in carbohydrate fermentation rather than in the test meal.

Table V shows clearly that fat is utilized as completely when taken into an active stomach as when taken into an empty one.

TABLE V

Fat Utilization: Quantity of fat recovered from colon nine hours after ingestion of a meal consisting of one hundred grams of butter, four slices of bread, two ounces of molasses, two hundred c.c. of skimmed milk. Each figure represents an average taken from two experiments made on two consecutive days

Subject	Fat recovered where two bananas were eaten one hour before the fat meal	Fat recovered where two bananas were eaten just after the fat meal
1	2.854 gms.	3.284 gms.
2	3.047 gms.	3.973 gms.
3	2.902 gms.	2.149 gms.
4	3.105 gms.	3.388 gms.
5	2.324 gms.	2.004 gms.
6	4.107 gms.	3.206 gms.
7	3.528 gms.	3.349 gms.
8	2.947 gms.	3.562 gms.
9	4.055 gms.	3.345 gms.
Average	3.207 gms.	3.140 gms.

Utilization of Carbohydrate: The subject followed the program described under Protein Utilization, this time substituting a meal rich in carbohydrate for the protein test meal, and eliminating the afternoon meal of bananas to avoid introducing any more banana starch into the experiment than necessary. The two bananas eaten in the morning were thoroughly ripe, thus containing little or no starch and being readily digestible.

Table VI gives the analytical method used and the results for this experiment. Evidently a banana pre-meal does not interfere with the carbohydrate utilization of the subsequent meal.

TABLE VI

Carbohydrate Utilization: Quantity of carbohydrate recovered from colon nine hours after ingestion of a meal consisting of 120 grams wheat crackers, two hundred c.c. milk and twenty grams of sugar. Colon washings hydrolyzed at 100° C. for two hours with 2% HCl and analyzed for reducing sugar by Benedict's method. Each figure represents an average taken from two experiments made on two consecutive days

Subject	Grams of sugar recovered from colon	
	Two bananas eaten before the test meal (one hour)	Two bananas eaten with the test meal
1	4.325 gms.	4.505 gms.
2	1.400 gms.	2.740 gms.
3	3.720 gms.	1.848 gms.
4	3.865 gms.	4.007 gms.
5	2.743 gms.	2.526 gms.
6	3.430 gms.	2.460 gms.
7	3.000 gms.	3.050 gms.
8	3.708 gms.	
Average	3.274 gms.	3.017 gms.

SUMMARY

The utilization of proteins, fats and carbohydrates was the same when bananas were ingested before the meal as when this fruit was eaten along with the meal.

FACTORS INFLUENCING BACTERIAL FLORA WITHIN THE LARGE INTESTINE

Since the report upon the destruction of yeast within the large intestine (Montgomery, Boor, Arnold and Bergeim (5)), Bergeim has been studying some of the factors contributing to the toxicity of the intra-intestinal contents. A detailed report of these findings will be published elsewhere. The authors wish here to show the influence of certain fruits upon the bacterial flora of the large intestine.

Bergeim has shown that one of the most toxic substances for yeast and B. coli found in the large intestine is butyric acid. Hydrogen sulphide ranked next in importance as a bactericidal agent for certain bacteria. We have used the contents of the large intestine obtained by enema, using 3000 c.c. of washing fluid, divided into two equal portions. The solid and fluid portions of the suspended fecal material were analyzed separately for hydrogen sulphide and butyric acid content. Direct smears stained by Gram's method were made from the mixed washings.

Three subjects were maintained for four days on the following diet:

Breakfast: Three fried eggs, four strips bacon, two pieces of toast with butter, juice of ½ lemon in a glass of water sweetened with cane sugar.

Luncheon: ½ pound of ground beef fried, four slices of bread, butter, honey, tea.

Supper: ½ pound ground beef fried, gravy, potatoes, bread, butter, honey, lemon juice.

During the four days the urine was tested for indican twice daily by shaking with chloroform and Obermeyer's reagent. Bowel movements were recorded. On the afternoon of the fourth day a high enema was given, two successive washings each with 1500 c.c. of sterile water. The washings were then analyzed quantitatively for butyric acid and hydrogen sulphide. B. coli counts were also carried out on the same individual. This program was then repeated, all conditions being the same with the exception that two bananas were eaten an hour before each regular meal and two more before retiring (eight bananas per subject each day), and the carbohydrate content of the regular meal was reduced in proportion.

Hydrogen sulphide was determined by blowing over the gas with a current of hydrogen into alkaline lead acetate-gelatine solution and comparing colors obtained with those obtained with standard hydrogen sulphide solutions (6). Butyric acid was determined by extracting 200 c.c. portions of the washings (previously acidified with sulphuric acid) three times with 1000 c.c. portions of ether, distilling off the ether, adding 50 c.c. of water and distilling off the volatile fatty acids which were then determined by the isopropyl ether partition method of Osburn and Werkman (7). These methods will be discussed further in another connection.

Table VII gives the results of this experiment. It will be noted that there was a marked reduction in the indican in the urine, decrease in the hydrogen sulphide in the colon washings, and an increase in the butyric acid content of the large intestinal contents after banana ingestion. Correlated with the increased butyric acid content was a relative decrease in the viable B. coli in the washings. The gram positive to gram negative ratio of direct smears from the washings showed a preponderance of gram positive forms following the banana diet. Considerable work has been done in this laboratory in conjunction with the Department of Pediatrics on the bacterial flora of feces of infants fed various carbohydrates. We were unable to show banana powder influenced in any way the gram positive to gram negative ratio. This will be reported in the near future. The observations included in Table VII were washings from the large intestine and hence the bacterial flora may differ from that found in formed feces.

The results reported in this experiment substantiate Bergeim's work. He has shown that *in vitro* as well as *in vivo* experiments the concentration of butyric acid in the large intestine was perhaps the most important single factor in reducing the number of viable bacteria.

SUMMARY

On the high banana diet, amounts as high as 578 c.c. of 0.1 N butyric acid were found in the colon and the average amount was 329 c.c. The amounts found in the upper colon averaged 194 c.c. of 0.1 N butyric acid. Following the enemas of 3000 c.c. of water, the average recovery of material was 3100 c.c. The bulk of material as it existed in the colon and hence the concentration of butyric acid in the colon cannot be accurately estimated from these findings. However, the

TABLE VII

Effects of eating two bananas before each regular meal and before retiring. Diet No. 1, bananas eaten; Diet No. 2, no bananas eaten.

Subject and Diet	Day	Bowel Movement	Indican in Urine	H_2S (free) c.c. 0.001 N.	Butyric acid c.c. N/10	Gram + Gram −	Content of Colon washings. Millions of B. Coli in washings
No. 1 A. H.	1	1 large soft	slight	in liquid	in liquid		in liquid
	2	1 large soft	slight	189	179		30,000,000
	3	1 large soft	none	in solid	in solid	80	in solid
	4	1 large soft	none	30	64		
No. 2 A. H.	1	1 large soft					in liquid
	2	none	moderate				498,000,000
	3	none	strong			0.4	
	4	discontinued experiment (headache)	strong				in solid 40,000,000
No. 1 E. H.	1	1 large soft	slight	in liquid	in liquid		in liquid
	2	1 large soft	none	292	130	6.4	131,000,000
	3	1 large soft	none	in solid	in solid		
	4	1 large soft	none	16	36		
No. 2 E. H.	1	1 large soft	slight	in liquid	in liquid		in liquid
	2	none	strong	700	51	1.2	498,000,000
	3	none	strong	in solid	in solid		
	4	none	strong	44	24		
No. 1 L. B.	1	1 large soft	slight	in liquid	in liquid		in liquid
	2	1 large soft	slight	178	274	5.5	150,000,000
	3	1 large soft	slight	in solid	in solid		
	4	2 large soft	slight	30	304		
No. 2 L. B.	1	1 large soft	slight	in liquid	in liquid		in liquid
	2	1 small hard	strong	356	74	0.2	1,080,000,000
	3	none	strong	in solid	in solid		
	4	none	strong	47	61		

average amount of material in the intestines can hardly have been much over 300 c.c. on the average, and the concentration of butyric acid not much less than 0.1 N. The pH values of the contents of the upper colon were between 6.0 and 6.5. In *in vitro* experiments it has been shown that concentrations of 0.05 N of butyric acid at pH 6 reduced the growth of B. coli to about 1/100th of that in the control, and that at pH 6.5 a reduction of growth to 14% of normal was obtained with 0.1 N butyric acid. The decreased number of B. coli in the intestines on the banana diet might therefore be accounted for by a limitation of growth by the butyric acid present, assisted by acetic acid also present, though these need not be the only factors concerned.

On the banana-free diet, on the other hand, the butyric acid concentrations were much lower, and the pH so near neutrality that no inhibiting effect of butyric acid on B. coli would be expected. This agrees with the high counts of B. coli found on these diets.

It appears therefore that the reduction in the numbers of B. coli on the high fruit diet was at least in part due to the increased production of butyric acid on this diet, associated with the lowered pH.

HABITUAL FRUIT PREMEAL

The use of the fruit premeal was started in order to test gastric response to the fruit alone, free of any other form of food. There were certain advantages, both in gastric and intestinal bactericidal function, shown to follow the ingestion of a small amount of fruit one hour before the regular meal. It has been shown also that this does not interfere with the utilization of fats, carbohydrates and proteins of the subsequent meal. It was thought necessary to test the general reaction of a group of normal adults to the habitual use of a fruit premeal.

Ten subjects have been on a banana premeal for fourteen weeks. Two bananas were eaten one and one-half hours before lunch, before dinner, and just before retiring at night. A daily report was made on bowel movements, gastric and intestinal disturbances, gas, discomfort, fatigue, both mental and physical and appetite. Weight was recorded twice weekly. No ill effects were noted by any subject. Three of these ten subjects had been constipated. After six to eight days on the banana premeal, bowel movements occurred daily, with large soft stools. Four of the ten subjects recorded noticeable gas in the large intestine the first three days on the premeal diet, but none after this time. The appetite was not affected. There may have been less mental and physical fatigue, particularly before lunch and dinner time. Our object was to see if any abnormal reactions would be noticed by people on a fruit premeal for several months. No disadvantages were found. Three months after this experiment was stopped, six of the eight adults are continuing the banana premeal habit; the reasons they give are regular bowel movements, and lessened mental and physical fatigue.

TABLE VIII

Two bananas eaten one and one-half hours before meals and before retiring at night each day. Otherwise diet and general habits unchanged. Record of weight after 4 months

Subject	Sex	Age	Beginning Weight	Weight after Four months
D. K.	M	58	184	181
D. K.	F	53	135	133
L. S.	F	40	132	136
A. J.	F	34	198	195
S. M.	F	25	131	135
E. R.	F	38	127	127
V. S.	F	27	100	103
E. G.	F	25	128	125
M. G.	M	8	67	70
B. G.	M	12	86	91

INFLUENCE OF FRUIT PREMEAL ON FOOD ALLERGINS

The authors realize that allergy to foods is a very big subject and is now receiving considerable attention. It is not our purpose to deal with the disputed mechanism of this reaction, but we wish to record some observations we have made using the fruit premeal to produce an actively digesting gastric environment at the time the specific sensitizing substance was ingested. It seemed logical to assume that if the anti-

TABLE IX

The peptic power and pH of gastric contents one hour after the ingestion of one banana, one apple, one orange, and 100 c.c. of chicken broth, respectively. Peptic power = number of mm. of egg white digested in 4 hours (Mett's test)

Subject	Banana		Apple		Orange		Broth	
	pH of Chyme	Peptic power	pH of Chyme	Peptic power	pH of Chyme	Peptic power	pH of Chyme	Peptic power
A. H.	1.4	1.8	1.4	1.8	1.6	1.8	1.8	1.8
E. G.	1.8	1.8	2.0	1.8	1.4	1.8	2.0	1.8
L. B.	1.6	1.7	2.0	1.8	1.8	1.8	2.0	1.9
W. B.	1.9	1.9	2.0	1.8	2.0	1.9	1.6	1.8
Average	1.7	1.8	1.8	1.8	1.7	1.8	1.8	1.8

genic protein causing the food sensitivity was hydrolysed rapidly in a gastric lumen containing free acid and pepsin, then the phenomenon of hypersensitivity to the specific protein substance might be reduced or it may be possible that the reaction would not occur. We wish to report our experiences and observations as far as we have carried them.

The destruction of the sensitizing antigen in foods by gastric digestion would depend upon the presence of pepsin. We therefore determined the relative peptic digestion of aspirated gastric contents after the ingestion of fruits. Table IX gives the results using four healthy subjects.

One banana was ingested by a fasting, young, normal adult. The gastric contents were aspirated after one and one-half hours. This material (pH. 2.0) was used to digest rag-weed pollen protein, one hour incubation at 40° C. The tests were set up as follows: 0.2 c.c. pollen extract plus 0.8 c.c. gastric banana contents; incubated one hour at 40° C., then brought to a pH of 7.1 by addition of sodium carbonate. This digest was then used as antigen for skin tests on known sensitive patients. The first two columns in Table X give the results of two separate experiments, run with different pollen extracts and gastric juice from two different normal subjects. The third column in Table X consists of the following: 0.8 c.c. gastric contents after banana ingestion (pH 2.0) brought to pH 7.1 with sodium carbonate. The fourth column in Table X are the results using the following antigen: 2.0 c.c. pollen extract plus 0.8 c.c. 1/10 N. hydrochloric acid and incubated one hour at 40° C., then brought to pH 7.1 with sodium carbonate. The fifth column are the results from the following antigen: 0.2 c.c. pollen extract plus 0.8 c.c. disodium phosphate incubated one hour at 40° C., reaction adjusted to pH 7.1. The last column represents the skin reactions after boiling the pollen extract and adjusting to pH 7.1 with sodium carbonate.

There were several ways of approaching this problem. We began by digesting the specific food with gastric juice as outlined in the experiments using ragweed pollen. We thought these results might not be conclusive, so we next resorted to the use of the human stomach. It is well known that the allergic reaction following ingestion of a given specific food substance is variable, at times it may be absent, this is probably rare, but there are many degrees in the intensity of the hypersensitive reaction. We realized we did not have sufficient time at our disposal to do enough actual feeding experiments on food allergic cases to obtain the most desirable information. We therefore decided to use the skin testing technic and digest the antigenic material in the gastric lumen of normal subjects. The specific food substance to be investigated was ingested into a fasting stomach and aspirated fifteen minutes afterwards. The other series of antigens were prepared by ingesting one banana and, after one hour, eating the same amount of the same specific food and aspirating after fifteen minutes. Two antigens were used for skin tests on susceptible patients. One had fifteen minutes contact with an empty stomach, the other after fifteen minutes contact with an active digesting stomach. The gastric aspirations from the fasting stomach were diluted three times with buffered phosphate solution and adjusted to pH 7.1 with solid carbonate. The gastric aspirations from the premeal digesting stomach was diluted the same, and the reaction was adjusted to pH 7.1 with solid sodium carbonate. The physical consistency and intensity of reaction caused us to use this method of procedure.

The specific foods tested were blue-berries, peas, milk, beans, radishes, walnuts, hazel nuts, strawberries, beef and rye bread. The Allergy Clinic of this institution cooperated with us in placing patients sensitive to these food substances at our disposal for study. Table XI gives the results of our observations. The short time interval of 15 minutes was chosen as our preliminary test. It has been necessary to discontinue our work, and longer digestive periods have not been carried out as was originally planned.

SUMMARY

A fruit premeal offers a method of reducing the irritating properties of food allergins. Our results can only be offered as preliminary studies, but are encouraging enough to warrant further observations.

DISCUSSION

We became interested in the premeal, or between meal, fruit feeding because of certain observations

TABLE X

Skin reactions performed on eight ragweed sensitive patients with various modifications of the antigen

Subject	Pollen Digest	Pollen Digest	Control Gastric Contents	Control Pollen Acidified	Control Pollen Neutralized	Control Pollen Boiled
1	0	0	0	10	10	10
2	0	0	0	10	10	10
3	0	0	0	30	10	10
4	75	30	0	10	10	10
5	0	0	0	10	10	10
6	60	35	0	10	10	10
7	0	0	0	60	10	10
8	0	0	0	10	10	10

0 = no skin reaction.
The numbers represent time in minutes when positive reaction appeared after intradermal injection.

made during fasting periods of the day to determine the gastric pattern of reaction which would follow the ingestion of fruit alone. We observed a prompt response on the part of the stomach to ingested fruits. The banana causes a rapid concentration of acid and pepsin after ingestion. The banana is buffered very well, and requires a relative large amount of acid to completely acidify. The progressive accumulation of

TABLE XI

The influence of a fruit premeal upon the antigenicity of food allergins. The specific allergic food (column 2) was ingested by a normal subject. One sample was ingested after arising in the morning (column 3), one sample was eaten one hour after one banana was ingested (last column). Fifteen minutes after ingesting the specific food the gastric content was aspirated and each sample used as antigen for skin testing of known allergic patients (column 1)

Hypersensitive subject	Specific food ingested by normal subject	Skin reaction to Antigens prepared from: Contents of fasting stomach. 15 min.	Skin reaction to Antigens prepared from: Contents of fruit premeal stomach. 15 min.
T. M.	Blueberries (canned 50 grams)	++++	0
W. F.	Peas (juice of canned 50 c.c.)	++++	0
W. F.	Peas (solids of canned 50 grams)	++++	++++
D. W.	Milk (fresh, pasteurized whole, 200 c.c.)	++++	0
S. F.	String beans (solids of canned, 50 grams)	++	0
C. A.	Radishes (fresh, 50 grams)	++++	++++
L. W.	Walnuts (10 grams)	++++	++++
A. V.	Hazel nuts (liquid part of digest, 10 grams)	++++	0
A. V.	Hazel nuts (solid part of digest, 10 grams)	++++	++++
A. N.	Strawberries (fresh 30 grams)	++	0
H. R.	Beef (ground, baked, 100 grams) (liquid part of digest)	+++	0
	(solid part of digest)	++++	++++
G. P.	Rye bread (50 grams)	+++	0
L. C.	Beef, broth (100 c.c.)	++++	+

acid after ingestion of fresh bananas has a "protein-like" gastric pattern, similar to the free and combined acid figures one encounters so frequently after a protein test meal. We became interested in the between meal feeding of fruits from a bacteriological and public health standpoint. We were primarily interested in the passage of orally ingested bacteria through the gastric barrier, and reaching the large intestine in a viable state. This led us to study in greater detail the relationship between gastric acidity and viable bacterial flora within the lumen of this organ.

The influence of a fruit premeal on the ability of the stomach to destroy ingested bacteria in the subsequent meal was considered an important protective mechanism. The same intra-gastric environment produced by the fruit premeal could rapidly acidify and alter protein complexes capable of causing supersensitive reactions in susceptible persons. The influence of this mechanism on food allergy must be investigated by clinicians familiar with this field. We have shown that the gastric content after a fruit premeal can rapidly render the sensitizing substance non-antigenic or non-allergic.

Holmes, Pigott, Sawyer and Comstock (8) and later Comstock and Eddy (9) studied the effect of vitamin A on absence due to illness among industrial employees. The first named group used cod liver oil, but Comstock and Eddy used banana and milk, and their work, therefore, is in fact a fruit-milk premeal study in which factors other than the vitamin A of these foods is a possible factor in the reduction of illness that both studies show.

Haggard and Greenberg (10) have investigated the problem of diet in relation to physical efficiency, and have concluded that between meal feeding increases physical efficiency. They report a freedom from a feeling of fatigue, irritability and from muscular inefficiency when their subjects ingested food at more frequent intervals than the standard three meals a day. The three meal feeding habit of man is not considered physiological by these observers. In addition to muscular efficiency and muscular effort, Haggard and Greenberg investigated efficiency in relation to blood sugar level and respiratory quotents. The following quotation from the above workers illustrates the relative importance of the premeals or between meal. "Our conception of the 5-meal-a-day schedule calls for the conventional 3 meals with the addition of 2 smaller meals: mid-morning and mid-afternoon lunches. But on such a schedule, as on any other, no one meal stands alone in the diet; each is merely a part of the total daily intake of food and should be planned with the total in view. From the dietetic point of view, the food eaten at the 2 extra meals is not to be added to that of the regular meals, but subtracted from them; it is merely eaten at another time. Due provision must thus be made that the selection of food for the smaller meals is properly supplementary to the larger meals."

The "between meal," or as we have termed it, premeal, seems to have received attention from various angles within the last couple of years. The vitamin, calcium, etc., content as supplementary feedings, the influence upon physical efficiency and their possible significance from the viewpoint of efficient gastro-duodenal bacterial killing function as well as aiding in reducing food allergeries.

The gastro-duodenal bactericidal mechanism has been studied in this laboratory for several years. Our primary interest in the fruit premeal was to study its effect upon this mechanism. During the course of the investigation, Bergeim has shown a bactericidal action in the large intestine which can in part be explained by the presence of butyric acid. Bergeim has already shown these substances exert a bactericidal action in *in vitro* experiments. There are then at least two bacterial controlling mechanisms, the gastro-duodenal, depending to a great extent upon hydrochloric acid secretion by the stomach with complete saturation of the gastric contents with acid. The bacterial controlling factor in the large intentine is dependent upon the presence of butyric acid and the more acid contents, which are associated with a lower bacterial count of the washings from the large intestine.

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SECTION IV—*Roentgenology*

Newer Interpretations of Gall Bladder Function and Their Diagnostic and Therapeutic Application*†

By

MAURICE FELDMAN, M.D.‡

and

SAMUEL MORRISON, M.D.§

BALTIMORE, MARYLAND

IN a previous communication one of us has described some anatomic changes that occur in the filled gall bladder as shown by cholecystographic study. This method of examination also lends itself admirably to an understanding and correlation of the physiologic changes. The physiologic mechanism of contractility of the gall bladder has been studied by many investigators, notably by Boyden (1), Whitaker (2), Ivy (3), Graham (4) and others.

In a recent presentation on the subject of cholecystography a plea was made for a uniform and simple technic (5). In the present study we have further simplified the test by diminishing the time interval following the fat meal. We have selected in this study a group of 61 cases in which poor contractility or an absence of contraction of the gall bladder was observed following a fat meal.

The fat meal utilized, consisted of two eggs and a glass of milk, mixed in a shaker and given as a milk-shake. In order to be certain that a uniform meal of sufficiently high fat content is taken, the meal is administered by the technician. The roentgenologist is then assured that the patient has taken the meal, that it has been retained and furthermore admits of a correct estimation of the meal interval. An attempt will also be made in this publication to correlate the roentgen findings of our cases with the clinical manifestations and the results obtained from the examination of the bile following non-surgical biliary drainage.

The importance of determining the degree of contractility of the gall bladder in a cholecystographic study is emphasized, since, according to our experience, disturbance of this function often produces a train of digestive symptoms and changes in the gall bladder bile which point to pathology of this organ and also to a method of successful therapy in many instances.

For many years it has been known that following the ingestion of certain foods, a definite effect upon the contractility of the gall bladder is produced, causing it to empty.

There is no unanimity of opinion among roentgenologists as to the optimum time interval for the examination following the administration of a fat meal. Although many roentgenologists have chosen the one hour period, others have made the examination at varying periods ranging from one to three hours.

Normally, the gall bladder when filled with an opaque medium, will show an appreciable contraction following a fat meal. The initial contraction begins in from five to fifteen minutes, reaching its initial maximum contraction in thirty minutes. The degree of contractility of the normal vesicle is usually marked, the volume diminishing to less than half, most often to between one-third to one-twentieth of its original size, while in the pathologic state the degree of contraction is lessened to a marked degree and frequently little or no contraction occurs, depending no doubt, upon the

*Read by title at the 35th Annual Meeting of the American Gastro-Enterological Association, Atlantic City, N. J., June 10, 1935.
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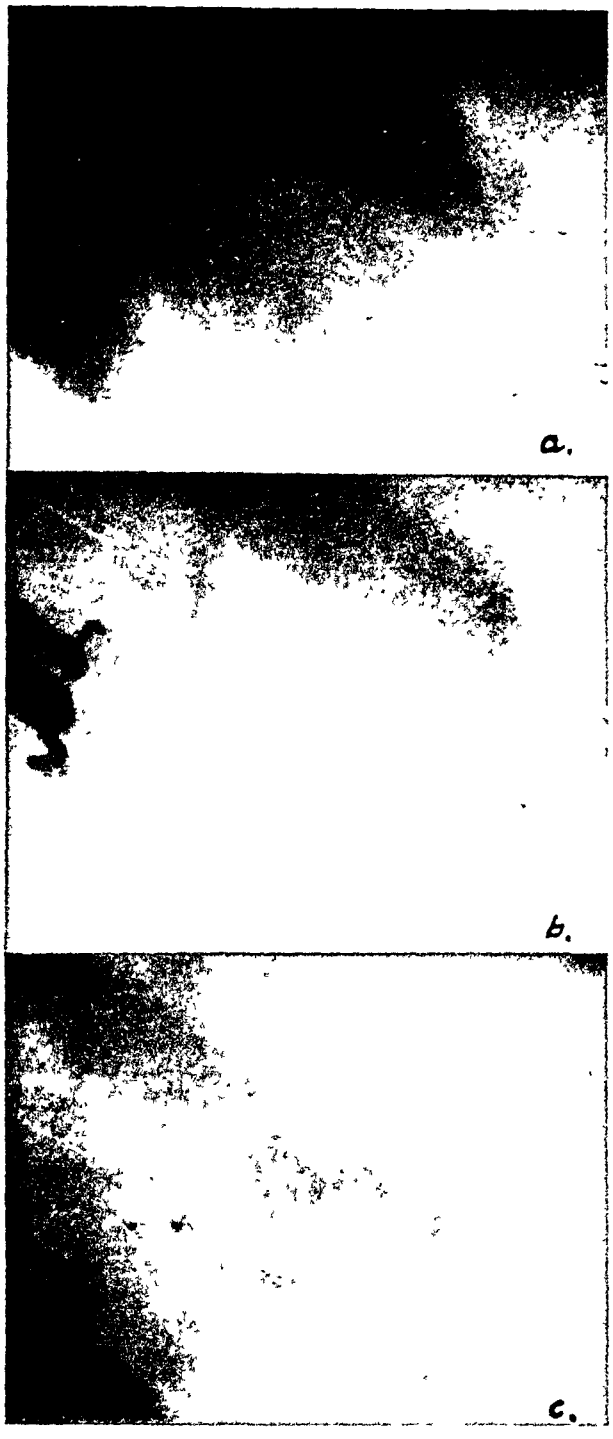


Fig 2. Illustrative case. (Miss M. M.) Showing no contraction following a fat meal. a. Dilated non-calculous gall bladder. b. 30 minutes following a fat meal, no response shown. c. One hour following a fat meal, showed no contraction of the gall bladder.

contracted to two-thirds and two to three-fourths of its original size. Our experience has shown that the roentgenologic examination one-half hour after a fat meal usually suffices. The test is completed after this period, thereby lessening the time consumed in the examination. Examinations of longer periods may be carried out if desired.

As a result of this study, hyperirritability of the gall bladder suggested itself. It probably represents another type of gall bladder dysfunction, characterized by a too rapid emptying. For some years we have routinely made examinations of the gall bladder one hour after a fat meal and in many instances have found the vesicle to be empty of its opaque medium, though the majority of cases showed a vesicle shadow. Just why a small percentage of gall bladders become non-visible was never quite understood. One of the reasons may have been the one hour examination, which is too long an interval for the study of functional disturbances. Thus, in a group of 302 cases of well filled gall bladders, 47 revealed an absence of shadow one hour after a fat meal. No abnormal interpretation was made of this finding as it had occurred in a normal appearing gall bladder. We believe, however, that when the vesicle shadow becomes invisible one-half hour after a fat meal, in a gall bladder which fills normally, one is justified in interpreting this finding as a hyperirritable condition of the gall bladder. Complete emptying of the vesicle as evidenced by absence of the gall bladder shadow one-half hour after a fat meal is an uncommon observation. It occurred in only one instance in another group of cases which are not considered in this presentation.

Clinical study: The non-calculus gall bladder in which the cholecystographic study shows slow emptying does not produce attacks of pain as one sees in gall bladder colic nor is it associated with atypical attacks of pain. Gas is a very prominent symptom, manifesting itself in the form of belching, abdominal distention and pressure sensations. Epigastric distress and discomfort and soreness in the right upper quadrant are very common. Other symptoms which occur fairly frequently are constipation, "acidity," bitter taste, dizziness and nervousness. Inasmuch as there is usually no duct obstruction, jaundice is not observed, but there is enough disturbance in the biliary system to produce definite symptoms. Bile in the urine is rare in these cases and even when the symptoms were at their height there was no evidence of bilinuria. A striking finding is the hepatic enlargement. It is noteworthy that our records show the liver edge distinctly palpable in 18 cases and the liver distinctly enlarged in six; in thirty-seven it was not palpable.

Sex: There were thirty-seven females and twenty-four males in this series. The ages ranging from 21 to 70 years. It is noteworthy to observe that the largest percentage occurred between the ages of 40 and 50.

Duodenal drainage findings: Of the sixty-one cases in this series biliary drainages were obtained in twenty-one instances. In twenty, the bile was turbid, cloudy, and stringy mucus intimately mixed with the bile was found in abundance. In only one instance was the bile recorded as clear, but this drainage was incomplete. Only an occasional w.b.c. was seen and rarely crystals. There was always an excessive flow of thick mucus in the cases drained and sometimes the mucus was so thick that the drainage tube became obstructed. It is of interest to note that of the twenty-one cases drained, relief of symptoms was observed in eighteen instances, while in three no relief was noted. The presence of abundant mucus in these cases would suggest that the term "mucus cholecystitis" adequately expresses the condition and may give some conception of the mechanism of poor contractility. Frequently

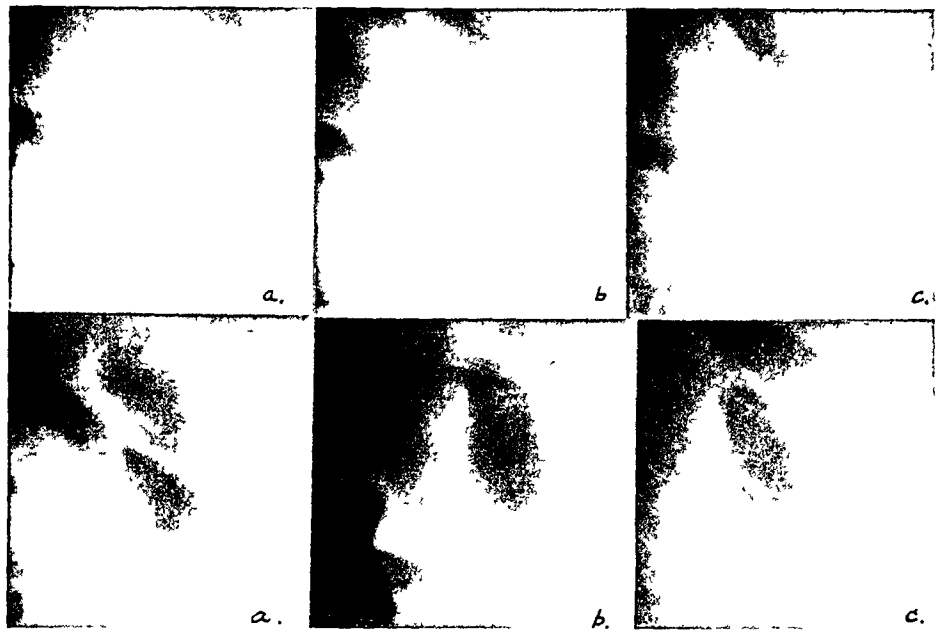


Fig. 3. Upper; a. shows a normal appearing non-calculous gall bladder. b. 30 minutes following a fat meal, gall bladder contracted to ¾ of its original size. c. One hour examination, no further contraction occurred. Lower; a. normal appearing gall bladder. b. 30 minutes following a fat meal; very little change in size is shown. c. One hour examination, size of gall bladder similar to that observed in 30 minute roentgenogram.

these cases are difficult to drain at first, but after repeated attempts and stimulations with magnesium sulphate they begin to drain. Later, the length of time or duration of the drainage is diminished and even though mucus may still be obtained, it apparently flows more readily and less tenaciously; the patient feels better. In one of our cases, the patient had had two gall bladder visualization tests before we saw him. In each instance the gall bladder was reported as not being visualized. In our hands it did visualize (larger dose of dye); it was found to contract poorly following a fatty meal. This patient was also difficult to drain, principally because mucus plugs formed in the tube. After many drainages his biliary system now empties in one hour, whereas formerly with more intense stimulation the drainage was hardly complete in three hours.

The usual sequence of events is as follows: only mucus and duct bile can be obtained at first, later liver bile and only after many trials is gall bladder bile obtained. Abundant mucus is secured with the gall bladder bile and later it becomes normal appearing "B" bile.

In the cases of the poorly functioning gall bladder presented in this study, the appearance of an excessive amount of thick stringy bile was a striking feature which was constantly present. This thick stringy mucus accounts for the variable cholecystographic changes which sometimes occur. It is not unusual in these cases to obtain a non-filling gall bladder during the stage when symptoms are active, while after the condition has subsided, the gall bladder will fill readily. This occurred in one of our cases which revealed excessive amounts of mucus.

CONCLUSIONS

1. The normal human gall bladder shows an initial maximum contraction within thirty minutes after a fat meal. After the second thirty minutes (one hour

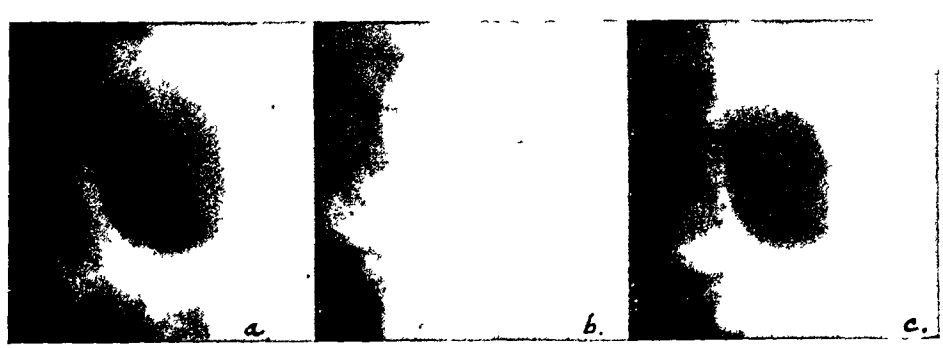


Fig. 4. a. A well filled non-calculous gall bladder. b. Poor contraction 30 minutes following a fat meal. c. Shows slight change in shape of gall bladder with but little further contraction one hour after the fat meal.

examination) very little or no further contraction occurs.

2. Our study would indicate an intermittent contraction of the gall bladder as a normal phenomenon.

3. In the routine cholecystographic test, the thirty minute examination following the fat meal usually suffices; this lessens the duration of the test.

4. The irritable gall bladder is discussed. This term is applied to the gall bladder which empties completely within one-half hour.

5. There seems to be a definite correlation in our series of cases, between the poorly contracting gall bladder and biliary drainage findings.

6. Of the sixty-one cases revealing poor contraction, twenty-one were drained by means of the non-surgical method of Lyon. Of these, twenty yielded abnormal drainage findings as evidenced by excessive amounts of thick mucus.

7. Of the twenty-one drained, therapeutically (i.e. a number of drainages at regular intervals). Complete relief from symptoms was observed in eighteen instances; in only three there was no relief.

8. For the type of affection being discussed, duodenal drainage is the treatment of choice, although surgical intervention sometimes may be indicated.

9. We have discussed a group of sixty-one non-calculus malfunctioning gall bladders and have suggested that the term "mucus cholecystitis" may be descriptive of those cases in which large amounts of mucus are obtained following non-surgical biliary drainage.

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SECTION V—*Therapeutics*

Clinical Results in the Medical Treatment of Chronic Ulcerative Colitis*

By

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IT is singularly difficult to compare the results of various forms of treatment for chronic ulcerative colitis because one of the chief characteristics of this disease is the variable severity of its manifestations. Furthermore, this variation in severity is probably the most important factor determining the final outcome of an individual case. For this reason, patients with ulcerative colitis who are observed in this Clinic are classified into three fairly distinct clinical groups for the purpose of studying the end results of treatment.

In Group I, are placed all cases which show no evidence of toxemia or systemic manifestations of colitis such as fever, leukocytosis, anorexia or vomiting. In grouping cases, no attention is given to the extent of the disease in the rectum and colon for two reasons: first, the limits of the morbid process as determined by the X-ray are uncertain, and second, close correlation between the clinical severity and the amount of colon involvement has not been observed.

In Group II, are placed those cases which, although they show no signs of toxicity, are found on examination to have marked permanent and irreparable damage of the colon, rectum or both. Patients with rigid contracted or stenosed bowels from long standing colitis fall into this group. Secondary anemia caused by chronic blood loss is not considered a sign of toxicity.

In Group III, are placed all patients who have fever or show other clinical evidence of toxemia, such as leukocytosis, nausea, vomiting, rapid pulse rate and prostration.

MATERIAL STUDIED

Fifty-five cases of ulcerative colitis observed and treated medically at this Clinic, were found to fall into the above classification as follows:

Group I (non-toxic, non-sclerotic)	23
Group II (non-toxic, sclerotic)	8
Group III (toxic)	24

The *treatment of ulcerative colitis* in this Clinic, has been the management of a chronic disease involving an inflammation of the rectal and colonic mucosa with varying systemic effects. Therefore, except in a small proportion of cases in which so-called "specific" vaccines and sera have been tried, the treatment has been essentially non-specific in character.

Rest in bed has been considered essential and a large proportion of the patients were treated for a time in the hospital.

The *diet* prescribed varied with the individual but in general was bland and contained comparatively little residue. Boiled milk was the basis of the diet in many cases, while in others milk appeared to increase the

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TABLE I

Clinical Group I. Afebrile Cases. "Nonspecific" Therapy

Satisfactory

Case No.	Sex	Age	Duration of Colitis	Complication	Duration of follow up	Clinical Results
12823	F	35	3 yrs.	None	1 yr.	Complete and continued remission
14044	M	54	25 yrs.	Anemia Achlorhydria	5½ yrs.	
23685	M	19	3 yrs.	None	14 mos.	
25183	M	47	10 mos.	None	4 yrs.	
25252	F	49	4 mos.	None	4 yrs.	
27941	F	40	4 yrs.	None	8 mos.	
28400	M	38	1 week	Duodenal ulcer	1 yr.	
42317	F	24	2 mos.	None	1 yr.	
43701	F	45	15 yrs.	None	1 yr.	
44521	F	11	16 mos.	None	10 mos.	
45560	F	50	5 weeks	None	8 mos.	
45677	M	38	2 yrs.	None	15 mos.	
29504	F	37	8 mos.	Recto-vaginal fistula	2 yrs.	Mild recurrence with recovery
34920	F	39	4 yrs.	None	15 mos.	
31400	F	26	1 yr.	None	20 mos.	
45464	F	30	1½ yrs.	1 small polyp	7 mos.	

Unsatisfactory

Case No.	Sex	Age	Duration of Colitis	Complication	Duration of follow up	Clinical Results
27734	F	23	2 yrs.	None	1 yr.	Repeated Recurrences
29003	M	12	1 mo.	Stomatitis Appendicitis	1 yr.	
39080	F	29	8 mos.	Acute appendicitis	18 mos.	No improvement
40429	M	54	2 mos.	None	14 mos.	No improvement
16562	F	25	8 mos.	Psychosis	3½ yrs.	Severe recurrence Death

[a] Summary

Satisfactory results	16	(76%)
Unsatisfactory results	5	(24%)
Total	21	

number of stools and the patients did better when milk was omitted. Meats, such as beef, lamb, liver and chicken were allowed early in the management. The vitamine content of the diet was fortified by the use of cream, butter, brewer's yeast, cod liver or halibut liver oil and orange juice. In some instances it was necessary to give consideration to food idiosyncrasies.

TABLE II

Group I. Afebrile Cases. Nonspecific Therapy—plus Vaccine

Satisfactory

Case No.	Sex	Age	Duration of Colitis	Complication	Duration of follow up	Clinical Results
15117[1]	F	26	1 yr.	None	5 yrs.	Complete relief
26160[2]	F	19	1 yr.	None	2 yrs.	

(1) Mulford's antibody globulin.

(2) Vaccine from another case.

Of the *drugs* used, bismuth and belladonna were most frequently employed. Opium was found useful in the severe cases. In many instances, it seemed advisable as a therapeutic test, to employ a course of antiamoebic drugs such as emetine, chiniofon or acetarsone. These drugs were used cautiously and on any indication of aggravation of symptoms their use was discontinued. Some patients appeared to be improved by acetarsone but it was impossible to conclude that this or other arsenicals had any definite value.

Colonic irrigations were not used in this group except for small amounts of yatren or tannic acid solutions which were instilled into the rectum in a few cases. Small starch and opium enemas were of some value in alleviating tenesmus.

For the secondary *anemia* which frequently occurred, iron, in the form of ferric ammonium citrate, Blaud's pills or ferrous sulphate, was administered. In the severe cases blood transfusions were used freely and parenteral injections of saline and glucose solution were extremely valuable.

Dilute *hydrochloric acid* was given with meals if an achlorhydria existed.

Surgical interference, in the form of transverse ileostomy, was resorted to only in those cases with increasing toxemia and were definitely failing under

TABLE III

Group II. Chronic Sclerotic. Afebrile

Satisfactory

Case No.	Sex	Age	Duration of Colitis	Complication	Duration of follow up	Clinical Results
14693	F	37	5 yrs.	Achlorhydria Stricture of rectum Rigid colon	5 yrs.	Complete and continued remission
24314	F	33	5 yrs.	Rigid colon	3½ yrs.	
27727	M	59	3½ mos.	Rigid colon	2½ yrs.	Improved
33721*	M	32	15 yrs.	Rectal Stricture	10 mos.	

Unsatisfactory

Case No.	Sex	Age	Duration of Colitis	Complication	Duration of follow up	Clinical Results
23507	F	50	8 yrs.	Rigid colon	2 yrs.	No improvement
32799*	F	35	5 yrs.	Polyposis Stricture of rectum	2½ yrs.	
28563	M	40	3 yrs.	Rigid colon	1 yr.	
46786	F	43	2 yrs.	Rigid sigmoid and rectum	6 mos.	

Summary

Satisfactory cases	4	(50%)
Unsatisfactory cases	4	(50%)
Total	8	

*Received Vaccine (cases 33721 and 32799)

TABLE IV

Group III. Toxic, Febrile Cases. Nonspecific Therapy

Satisfactory

Case No.	Sex	Age	Duration of Colitis	Complication	Duration of follow up	Clinical Results
14585	M	8	10 mos.	Allergic	5 yrs.	Complete and continued remission
25918	M	21	10 days	None	3½ yrs.	
33824	M	34	6 weeks	None	2½ yrs.	
41362	F	31	8 yrs.	None	1 yr.	
43118	M	49	1 mo.	None	1 yr.	
46425	M	15	9 mos.	None	6 mos.	Improved

Summary

Satisfactory	6	(38%)
Unsatisfactory	10	(62%)
Total	16	

Unsatisfactory

Case No.	Sex	Age	Duration of Colitis	Complication	Duration of follow up	Clinical Results
21039	F	48	2 mos.	None	1½ yrs.	Severe Recurrence
39273	F	32	8 yrs.	Rigid colon	4 mos.	
28889	F	65	1 yr.	Diverticulitis	1 mo.	No improvement
17705	F	37	1 yr.	Allergic	4 yrs.	
9385	F	26	2½ mos.	None	3 weeks	No improvement
46519	M	27	1 mo.	None	3 mos.	
3613	M	51	2 yrs.	Rigid colon		Died in the Hospital after ileostomy
6681	F	21	2 mos.	None		
43224	F	26	3 weeks	Fistula in ano		
4547	F	16	1 yr.	Appendicitis	5 yrs.	Died of colitis

medical treatment. As a life saving measure it was apparently deferred too long in some of the fatal cases. Even if done early, in some of the extremely severe, fulminating forms of the disease, it is improbable that ileostomy would have prevented death.

Particular attention was given to the *general hygiene* of patients with ulcerative colitis. *Foci of infection* were searched for and treated. After leaving the hospital, patients were warned to avoid indiscretions in diet, fatigue and acute infection.

To speak of cures of this condition appears to be presumptuous as it does not take into account the characteristic tendency to spontaneous remissions and exacerbations.

The best results are therefore designated as complete and continued remissions. The next most satisfactory cases are those who obtained complete remission of symptoms but later have had a mild recurrence from which they recovered and are clinically well at this time. A third group also considered to be satisfactory end-results are those patients who are greatly improved and are carrying on their occupations but still have some evidence of colitis such as four or five loose stools daily.

The *unsatisfactory results* include patients who were completely relieved by treatment but later suffered a severe and disabling recurrence, or those who received no appreciable benefit from treatment, or those who died of the disease while under treatment.

Although so-called *"specific" forms of therapy* were used in twelve cases, it was found difficult to determine their value. Vaccines were prepared from organisms recovered from stools of cases of ulcerative colitis which conformed morphologically and culturally with the organism described by Bargen as the specific etiologic agent. Hypodermic injections of vaccines in gradually increasing doses were carried out over considerable time in a few cases.

In a few of the acute toxic cases anti-ulcerative colitis serum now on the market was employed without convincing benefit.

The cases observed in this Clinic are grouped in the accompanying tables according to their clinical classification and according to the type of therapy they received. Tables No. 1 and No. 2, show that the prognosis of chronic ulcerative colitis in the mild, afebrile and uncomplicated form is excellent. Seventy-six percent of this group recovered under non-specific therapy. Since only two cases were treated with vaccines the place of this therapeutic measure was not sufficiently evaluated. However, the recovery of these two cases brings the percentage of good results in this type of case up to 78.

Table No. III demonstrates that one-half of patients with irreparably damaged bowels can be relieved by non-specific measures. It is surprising that normal bowel function can be even approached with the

TABLE V

Group III. Toxic, Febrile Cases. Nonspecific Therapy plus Vaccine or Serum Therapy

Satisfactory

Case No.	Sex	Age	Duration of Colitis	Complication	Duration of follow up	Clinical Results
16930[3]	M	46	1 yr.	Dermatitis of perineum	5 yrs.	Complete relief of Symptoms
36741[2]	M	50	7 yrs.	None	1½ yrs.	

Summary

Satisfactory	2	(25%)
Unsatisfactory	6	(75%)
Total	8	

Unsatisfactory

Case No.	Sex	Age	Duration of Colitis	Complication	Duration of follow up	Clinical Results
7529[1]	M	48	26 yrs.	None		Died in Hospital after ileostomy
17706[4]	F	20	10 weeks	None		
38567[5]	M	20	2 mos.	Hemorrhage		
[6]	M	32	3 weeks	Hemorrhage		
38872[5]	M	22	1 mo.	Jaundice		
33353	M	31	5 weeks	None		Severe recurrence

(1) Autogenous vaccine. (Diplococcus)
(2) Vaccine prepared from Mayo Clinic strain.
(3) Lilly's vaccine. (ulcerative colitis)
(4) Mulford's Antibody globulin.
(5) Parke Davis antiserum. (ulcerative colitis)
(6) Mayo Clinic antiserum. (ulcerative colitis)

amount of scar tissue that may be present in the intestinal wall of patients in this group.

It is in the third or the toxic afebrile group that the poor therapeutic results and the mortality of ulcerative colitis become apparent. In Table No. IV is shown that with non-specific therapy in only 38% of cases can results be called satisfactory. The mortality in this group of sixteen cases was 25%. In Table No. V the results in eight cases in which "specific" vaccines or anti-sera were used are tabulated. Two patients in this group who received vaccine recovered but anti-serum failed to save any of those in which it was tried. A remission occurred in Case No. 33353, following vaccine medication but a severe recurrence which was not relieved by serum necessitated an ileostomy. The mortality of this group of eight cases was 62%.

The *collective results* of the entire series studied (55 cases) are as follows:

Satisfactory	30	(55%)
Unsatisfactory	25	(45%)
Total	55	
Deaths	10	(18%)

DISCUSSION

A comparison of our results with those obtained in other Clinics using "specific" or other forms of therapy is impossible. The clinical results reported in this paper indicate that the end-results of treatment are profoundly influenced by the relative distribution of cases in the three groups just described. This relative distribution may depend largely upon the diagnostic criteria used in differentiating between early, mild, ulcerative colitis and other forms of colonic irritation. Furthermore, if, by chance or by other reason, a relatively large number of very sick patients is treated the end-results will be more unfavorable regardless of the form of therapy employed.

Therefore, it is hoped that future reports on the results of various forms of treatment of ulcerative colitis will include some clinical classification of the cases similar to the one described here.

It is well known that a considerable proportion of all cases suffering from chronic ulcerative colitis have the disease in a comparatively mild form. Although this group complains of bloody diarrhea and show on proctoscopic examination the characteristic inflammatory reaction of the mucosa, the condition is essentially local. Clinical signs of systemic manifestations of the disease, such as fever, leukocytosis or prostration, are usually lacking. The remaining cases of ulcerative colitis are characterized by abundant clinical evidence of systemic effects of the disease. Fever and other signs of toxemia are present in some cases from the onset, while in others they may be preceded by a period when only local signs were manifested.

It is interesting to speculate on the significance of these two groups. The existance of the afebrile group suggests that ulcerative colitis may be originally a non-infectious disease and that the onset of fever and toxic signs indicates the point when the resistance of the bowel mucosa is so broken down that secondary invasion by organisms within the intestine takes place.

It must be admitted, however, that convincing proof either for or against this concept is lacking.

SECTION VI—*Abdominal Surgery*

A Review of 746 Gastric and Duodenal Ulcers*

By

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IN discussing the treatment of gastric and duodenal ulcers the question of gastric ulcer undergoing malignant degeneration has such an important bearing on both the medical and surgical management of this type of ulcer that one should state his views on this point. The opinion expressed by me is dictated by observation in the stomach clinic of the 4th Medical and Surgical Division at Bellevue Hospital. During the past eight years we have observed 746 ulcers and 10 carcinomas of the stomach or a total of 756 cases. Of the 746 ulcer cases 642 were duodenal and 104 gastric or a percentage of 14 per cent gastric as compared with duodenal ulcers. If the 10 gastric carcinomata are added to the gastric ulcers we have 114 gastric lesions and of these only 8.7 per cent are carcinoma. From a practical point of view the emphasis of gastric ulcer becoming malignant has been over stressed. In another communication (1) this subject was more fully considered. It is worth remembering that primary carcinoma of the duodenum does occur, but, so far there has never been a reported case of duodenal ulcer undergoing malignant degeneration. If ulcer is such a common forerunner of gastric carcinoma then

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it should occur occasionally in the duodenum. A review of the literature (2) has failed to reveal that it does occur.

The etiology of ulcer is unknown in spite of the vast amount of experimental work that has been done in recent years. There are certain factors that influence the development of peptic ulcer and these will be discussed.

Sex: It is a disease that affects the male more frequently than the female. This has been most forcibly brought to the attention of the medical profession in (3) the Quarterly Bulletin of the Department of Health of New York City issued in 1934 in which they analyzed the death rate from ulcer patients from 1900 to 1933 and found that the ratio of those dying from an ulcer in 1900 was one male to one female, which very strikingly emphasizes the marked increase in the incidence of ulcers in the male sex. Age: An ulcer may affect a patient at any age from childhood to senility. The most common period in which ulcers are noted is the period between thirty and forty years of age. In analyzing 671 cases of peptic ulcer admitted to the stomach clinic of the 4th Medical and Surgical Division at Bellevue Hospital we found (4) that 47 per cent of the patients afflicted with ulcer sought relief between the ages of thirty and forty years. Heredity: Ulcers do run in families. We have had as many as one brother and three sisters suffering from ulcers out of a family of five. It is not uncommon for a parent and child to present themselves for treatment. Occupation does not seem to play any part in the causation of an ulcer and when one analyzes a large series of cases it is noted that people in every walk of life from high executives, small business men, truck drivers to longshoremen suffer from this disease. Ulcer is definitely on the increase. Although we are not able to say what causes an ulcer we can tell you that your chance of developing an ulcer is greater than twenty-five years ago. I can prove that statement in two ways. When one takes the total number of ulcers admitted to Bellevue Hospital each year and compares it year by year from 1910 to 1935 with the total number of patients admitted each year one sees a gradual increase in the number of ulcer patients per year and when it is figured against the total admissions per year the percentage of ulcers increases yearly. In 1910 there were 33 ulcer patients admitted to Bellevue Hospital and there were 36,000 patients admitted that year. In 1934 there were 353 ulcer patients as against 59,000 admissions. If one adds the ulcers from 1910-1922 admitted to Bellevue Hospital it is found that ¼ of 1 per cent of the patients had ulcers. From 1922-1934 it is found that over ½ of 1 per cent of the patients had ulcers. In other words your chance of developing an ulcer has doubled in the past twenty-five years. The Department of Health Bulletin in 1934 gives the following death rate of peptic ulcer per 100,000 population: In 1900 the rate was 3.69 while in 1933 it was 6.77. In other words those that died from peptic ulcers in New York City has doubled from 1900-1933.

The diagnosis of a peptic ulcer can be made nearly as accurately from a carefully elicited history and physical examination as by rontgenological studies of the gastro-intestinal tract. Of course both are essential in the diagnosis and treatment of a patient suffering from an ulcer, but one should not be mislead by a negative rontgenological report in a patient with epigastric pain that radiates to the back or in a patient with tarry stools or hematemesis. It is well to emphasize that posterior duodenal ulcers are the ones that cause a rather severe pain which is referred to the back and also this type of ulcer frequently causes severe hemorrhage. In a high percentage of instances it is difficult or impossible for the rontgenologist to demonstrate the lesion in view of the fact that it is on the posterior portion of the duodenum and frequently adherent to the pancreas. Therefore, clinical experience must be combined with careful laboratory studies in the diagnosis as well as in the advise for the method of treatment to be followed by the patient with a peptic ulcer.

The treatment of a peptic ulcer is generally conceded by both internists and surgeons to be medical as long as symptomatic relief can be obtained by medical management. It is well worth stating that there is definite danger in prolonged medical treatment when symptomatic relief is not obtained. In the treatment of peptic ulcer one should remember that ulcers of the stomach respond more rapidly and more lastingly to medical treatment than do duodenal ulcers. From the experience we have had during the past eight years I feel that the chances of a gastric ulcer undergoing malignant degeneration is very slight. It is important to emphasize that at times it may be difficult to differentiate between a carcinoma and an ulcer of the stomach. If the patient is past middle life and the X-rays are suspicious of malignant degeneration then one is justified in treating the patient as a possible carcinoma. These instances of confusion between an ulcer and carcinoma are relatively infrequent in a large clinic. A gastric ulcer, if it be an ulcer, will usually respond rapidly to medical management and the patient will soon become symptom-free. On the other hand, if the lesion is a gastric carcinoma medical management will not give satisfactory symptomatic relief under dietary management. One should remember that duodenal ulcer occurs six to one in comparison with gastric ulcer.

It is not necessary to go into a detailed discussion of the dietary management but we follow the Sippy regime in our clinic. It is of course necessary for one to adhere to a diet for years if permanent relief is expected. Medications are not given in the clinic unless the patient does not respond on a restricted diet. Alkalies are used when indicated and we have used other medications such as gastric mucin, synodal, larostidin, vaccines both non specific and specific, foreign proteins, such as aolan and all have had a rather extensive trial. The different medications occasionally have a definite beneficial result but there is nothing specific in any ulcer medication that we have had the occasion to use. At the present time we have just begun using silicon dioxide following the work and suggestion of Dr. Henry Lee of the University of Cincinnati and it may be more beneficial than other medications.

It is essential to insist that any focus of infection be eradicated, including bad teeth, tonsils, or sinus conditions. It is not believed that these have any direct etiological bearing on the ulcer but they lower the general resistance of the individual and therefore make it more difficult for him to overcome the ulcer from which he is suffering. Also it is important that

the patient get at least nine hours rest a night and avoid as much excitement and tension as possible. Also obstaining from the use of tobacco is quite essential and alcohol should be used in moderation if not completely avoided.

When a patient ceases to be a medical problem and should be operated upon constitutes one of the most difficult decisions to make in an ulcer patient. We do not believe that a patient presenting himself for treatment with a six hour residue of 50 to 100 per cent of the motor meal at the end of six hours is a surgical problem until medical treatment has failed. In our experience about 70 per cent of these patients do satisfactorily if put on anti-spasmodic and Sippy diet. Most of the retention is due to a persistent pyloro-spasm and edema which is frequently overcome with belladonna and dietary management. Hemorrhage does not constitute an indication for surgery except in a selected group of patients and the classification of the hemorrhaging ulcers that we use seems to be of some practical value in the treatment of bleeding ulcers and therefore it will be given. They are divided into five groups: (1) Hemorrhage occurring in patients with peptic ulcer under competent medical management; (2) hemorrhage in cases operated upon for an acute perforation, or chronic ulcer, that has never hemorrhaged until months or years following operation; (3) hemorrhage occurring in ulcers that had previously been operated upon for hemorrhage and the patient has continued to have recurring hemorrhage postoperatively; (4) severe hemorrhage that has occurred in patients with negative, or very short gastric histories, and the patient never knew that he had an ulcer until the hemorrhage occurred; (5) patients admitted with hemorrhage and a long history of ulcer symptomatology but without regulated medical treatment.

In outlining the management of a severe hemorrhage it is most important to consider the history and clinical course of the patient. Obviously, in the first group of cases, surgical intervention is desirable after the patient has recovered from the acute hemorrhage and is properly prepared for operation. A fatality in this type of patient is unusual, but the diability from recurring hemorrhages constitutes a most discouraging problem from the patient's point of view. In the second group we have a more difficult condition to treat, as the patient has either had some form of excision, gastro-enterostomy or gastric resection; and unless these patients have had two or more hemorrhages a reoperation should not be considered as the hemorrhage has occurred in spite of previous surgery, and possibly as a result of the surgery; therefore, one cannot give the patient much assurance that the same thing may not recur. In the third group we have the most difficult type of patient to treat with which one is confronted. Some of these patients have had several operations, including resection, and in spite of multiple operations have continued to bleed, and for that reason one should hesitate before reoperating upon these patients in the hope of relieving a hemorrhage unless a definite marginal ulcer can be demonstrated, which is usually not done. In group four it can be seen that the patient may have a severe hemorrhage and die suddenly, although one should not infer that because a patient with a negative, or short gastric history before the hemorrhage occurs, will have a fatality as a result of it. This is the type of patient one is undecided whether it is best, after giving repeated transfusions, and the patient's condition is considerably improved, to operate or treat conservatively. When one operates early in this type of case the ulcer must be excised, even if a gastric resection has to be done; otherwise a surgical intervention is of no avail.

In the fifth group we encountered more misunderstanding than in any other because the surgeon usually thinks that the long history, plus a hemorrhage, warrants surgery, but such is not the case. These patients have not received any regulated medical care and it is unusual for them to be admitted for a second hemorrhage. The results from conservative treatment have been sufficiently encouraging not to recommend operation in the first hemorrhage.

The one indication for operating upon a patient with an ulcer is pain which cannot be overcome by any methods of medical management and persistent pain in a patient under adequate medical treatment means that the ulcer is usually adherent to some adjacent viscus. In duodenal ulcers the pancreas is most commonly adherent, but occasionally it may be the liver and in gastric lesions it can either be the pancreas or the liver. When an ulcer becomes adherent to an adjacent viscus it constitutes a definite indication for operation and that can only be determined by clinical course of that case. When one evaluates the pain from which the patient is suffering it is found not to be of the ulcer type but is more severe and penetrating and the intensity usually necessitates sedatives to sleep.

When one has reached the decision that a patient needs to be operated upon for an ulcer we are faced with what type of operation to advise for a peptic ulcer. Everyone is aware that the majority of authors advocate either pyloroplasty or gastro-enterostomy and report most excellent results from both. In considering operation I wish to call attention to a previous communication (4) from our clinic in which 114 postoperative cases were reviewed and I am giving at this time three tables taken from that report.

TABLE V

Why Was the Patient Operated?

Symptoms	Number	Per Cent
Uncontrollable pain	85	79
Obstruction associated with pain	10	9
Bleeding associated with pain	8	8
Obstruction alone	4	3
Obstruction and bleeding	1	1

TABLE VI

Type of Operation

Type		Number	Per Cent
Gastro-enterostomy with excision	2	85	77
pyloroplasty	1		
enterostomy	2		
Resection including dissociation of old gastro-enterostomy	2	11	10
Pyloroplasty		7	6.5
Simple excision		5	4.5
Dissociation		3	2

TABLE VII
End Results

Condition Cured	No. of Cases	Per Cent
Gastro-enterostomy	33	
Resection	4	
Pyloroplasty	1	
Excision	1	
Total	39	37
Benefited		
Gastro-enterostomy	10	
Pyloroplasty	2	
Dissociation	1	
Total	13	12
Unimproved		
No relief under one year	23	
Developed marginal ulcer	16	
Temporary relief with return of previous symptoms	13	
Died (ulcer complications)	3	
Total	55	51

These tables will readily show that our results from the conservative type of operation has been anything but encouraging. It is also worth while to draw your attention to the high frequency of gastrojejunal or marginal ulcer which we have encountered in the cases which we have followed. In another communication (5) for the first six years of our clinic we reported an incidence of 16.4 per cent of marginal ulcer following gastro-enterostomy. One may think we have used poor judgment in selecting our cases, but of the 746 cases we have observed in the clinic 577 cases were unoperated upon when registered for their first visit. Of this number only 61 or 10 per cent have been referred for operation which would indicate that we have used reasonable care and discretion in selecting our patients for operation. Of the 746 cases which we have had in the clinic they have made 13,996 visits which averages 18 visits per patient during this period, which would give us reasonable opportunity to personally observe and direct the regime for each patient to follow.

Unquestionably the type of operation that is done must rest with the individual operator and the indications that he encounters at the time of laparotomy. From our cases the most common condition that is associated with a duodenal ulcer is a chronic pancreatitis, and if the chronic pancreatitis exists a gastro-enterostomy is a most unsatisfactory procedure for the relief of pain. Therefore, I feel a sub-total resection is warranted in such cases. Also bleeding duodenal ulcers are more commonly encountered in the posterior portion of the duodenum, than in the anterior and for that reason excision of the ulcer is essential to effect a cure. That can only be brought about by a sub-total resection if the ulcer is placed on the posterior portion of the duodenum and adherent to the pancreas. In patients suffering from pyloric obstruction with a large dilated stomach, a gastro-enterostomy is a quite adequate operation but even in this type of case a marginal ulcer does occur. If then one operates upon the patient with a duodenal ulcer that is having repeated hemorrhages or a duodenal ulcer associated with chronic pancreatitis, a sub-total resection is the operation of choice. The mortality in a resection is no higher in the hands of those that have a reasonable experience in gastric surgery than is the general mortality following gastro-enterostomy at the present time.

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Electro-Cholecystocausis*

Preliminary Report

By

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THE acutely inflamed gall bladder presents a difficult problem to the surgeon. Immediate operation is dangerous on account of hemorrhage. Prolonged expectant treatment, unless the patient is improving, may lead to rupture of the gall bladder. Cholecystostomy, heretofore the procedure of choice in these cases, leaves a diseased gall bladder in place and necessitates, for the future welfare of the patient, a cholecystectomy. A method whereby the gall bladder could be treated at the time of cholecystostomy in such a manner as to lead to its obliteration, would avoid the danger of a second operation. Such a method by the use of electrosurgery has been devised, and is now being tested on animals.

METHOD

In dogs, at a preliminary operation, the gall bladder is traumatized by crushing with clamp. Three to five days later the wound is reopened. The inflamed gall bladder is attached with sutures to the abdominal wall, an opening made in the fundus, the contents evacuated. With the aid of a focussing headlight and special re-

*Electrosurgical cauterization of the gall bladder. For this term the writer is indebted to Paul J. McManus, S. J.
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tractors the whole mucosa of the gall bladder is thoroughly treated by fulguration and light contact coagulation.

It is essential that the whole mucosa of the gall bladder be destroyed by this process, otherwise regeneration will lead to formation of a permanent sinus. But it is also necessary that perforation of the gall bladder as a result of deep contact-coagulation be avoided. Thus the application of electrosurgical current must be through fulguration and light surface coagulation only. The heat from fulguration is intense, but localized and superficial. It is deep enough, however, to destroy the mucosa. The blackening by the charring effect of fulguration is an indicator as to the thoroughness of treatment. Drains are placed within the gall bladder; the sinus is allowed to heal slowly, and close by sclerosis.

RESULTS

In experiments with dogs (eight in number) the sinus has closed at the end of three to four weeks; and post-mortem examination has shown that the gall bladder has been obliterated. No damage to other structures has been observed.

Electro-cholecystectomy has been described previously (1, 2, 3). It was a modification of Pribram's (4) operation of "mukoklase," in which the gall bladder was split to the cystic duct, the mucosa treated with an ordinary cautery, the leaves of the gall bladder whipped together with sutures, and the abdomen closed without drainage. In electro-cholecystectomy the redundant portions of the gall bladder are trimmed away and the part remaining attached to the liver treated by fulguration and light contact coagulation. Contrary to Pribram, however, drainage is employed.

Thorek (5, 6, 7) has devised a procedure termed "cholecystelectrocoagulectomy," using deep contact coagulation instead of fulguration of the part of the gall bladder left attached to the liver; and peritonization of the tied stump of the cystic duct and the coagulated tissue on the gall bladder bed. He also does not drain.

Electro-cholecystocausis, as described, appears to be an original procedure, though chemicals like phenol have been used for cauterization of the gall bladder (8). Experiments indicate that the method carries very little risk, is not too difficult of application, obliterates the gall bladder by a procedure carried out with little more shock than cholecystostomy, and avoids the danger of a second operation.

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SECTION VII—*Surgery of the Lower Colon and Rectum*

The Technique of the Local Injection of Saline Solution for the Relief of Pruritus Ani*

By

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THIS communication presents the technique of the local injection of physiological saline for the relief of pruritus ani. This treatment has been devised by the senior author and has been mentioned in another communication although the technique has never been described in detail (Schatz, 1). The present paper aims to bring this simple procedure to the attention of the medical profession and, especially, to the general practioner.

Pruritus ani is a most distressing ailment and there is perhaps no affliction more difficult to relieve. Numerous methods of treatment have been suggested for the alleviation of this common complaint. These vary from the more simple measures which include local application of solutions or perirectal injections of phenol solutions (Goldbacher, 2), to the more formidable surgical procedures of severing the sensory nerves supplying the area.

The etiology of pruritus ani is diverse and includes important factors which are as yet undetermined.

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Submitted November 15, 1935.

The simplest classification of the numerous causative agents is a modification of that adopted by Pennington (3) and consists of two groups. The first includes all local conditions such as trichophyton, irritating anal and rectal discharges and the systemic disturbances as diabetes and jaundice. This group is really that of anal irritation and strictly speaking is to be distinguished from the second group of those with persistent and intractable pruritus for which no demonstrable cause can be elicted. This so-called "idiopathic pruritus ani" is the most frequent and despite the elimination of all known local and general causes, has been remarkably resistent to every therapeutic method. The treatment to be outlined has proven especially valuable in this obstinate group of cases and for this reason should have a particular appeal to the general practitioner.

TABLE I

Treatment of Pruritus Ani. Therapeutic Results Following Local Injection of Sterile Physiological Saline Solution

31 Cases Treated*			
Each Case Received Some Measure of Undoubted Relief			
COMPLETE RELIEF		PARTIAL RELIEF	
16 Cases 50%	Complete relief without recurrence	15 Cases 50%	*6 Cases*—Complete relief with recurrence within 2 to 6 months. No recurrence following second treatment.
			9 Cases—Kept comfortable, despite recurrences, by repeated treatment each 1 to 3 months as required.

*These cases were all of the idiopathic and intractable group of pruritus ani where the elimination of local and systemic factors failed to achieve any measure of relief.

TECHNIQUE

A 10 c.c. syringe equipped with a twenty-three gauge needle, seven-eights of an inch in length, is used for the injection. Sterile physiological saline is the solution employed.

Having placed the patient on an examining table, in the left or right lateral position with the lower leg drawn somewhat backward, the upper hip is allowed to tilt slightly away from the operator. A sheet is draped over the buttocks, allowing an exposure of three inches about the anus. A good source of light is essential, and for this purpose a head-mirror with indirect light will suffice, but better still is a direct source from a small portable "goose-neck" lamp placed to the side of the operator.

Preparation of the entire area is accomplished by cleansing with liquid soap and water after which alcohol is applied. The area is divided into four portions by projecting two imaginary lines through the anus: the first passing antero-posteriorly through the fold of the buttocks and a second extending laterally and at right angles to the first. The greatest pruritic involvement is usually about the posterior anal commissure therefore either posterior quadrant is selected for the initial injection. Consistent with the greater degree of involvement, this quadrant should receive a relatively large volume of the fluid. The site of injection is along the edge of the circumanal pigmented area, which is situated one and one-half inches external to the edge of the anus. After the needle has punctured the skin, the point is directed toward the rectum as the spoke of a wheel. The barrel of the syringe is lowered so that the shaft of the needle lies in a plane of subcutaneous tissue, parallel to the skin and is at right angles to the long axis of the rectum. The needle is inserted until its point approaches within one-half inch of the rectal wall. This method is contrary to the usual injection procedure where the shaft is directed parallel to the long axis of the rectum. Three to five c.c. of the solution are slowly injected. The solution enters the tissues encountering only a slight resistance comparable with that of an intravenous injection and causes no discomfort to the patient. The needle is withdrawn and the procedure repeated employing a somewhat smaller volume in the less involved quadrants until the total of ten c.c. has been injected into the perirectal tissues. A total volume of fifteen to twenty c.c. of solution may be required for cases with extensive pruritic involvement. Following the injection the anal region should be gently massaged by a pledget of cotton saturated with alcohol or disinfectant. This manipulation achieves a distribution of the fluid about the perirectal spaces.

The only sensation following the injection is a faint sense of fulness about the injected area and except for the slight discomfort caused by the introduction of this small gauge needle there is no pain. In hypersensitive individuals anesthesia at the site of injection can be secured by applying a drop of phenol to the skin followed by alcohol, although this is rarely required.

The patient experiences a measure of relief within two to four hours following the treatment. In our series there have been no instances in which some benefit has not been secured. Complete alleviation without recurrence is obtained in about 50 per cent of all cases. In a few instances it is necessary to secure this complete result by repeating the procedure within one week. This is probably due to the fact that the entire involved area was not originally contacted by the solution. Of the remaining cases about one-half have complete relief with a recurrence of the symptoms within two to six months. These usually suffer no recurrence following the second treatment. The remaining group of patients experience an undoubted benefit following the injection and although they are not completely relieved it is possible to keep them comfortable by repeated injections administered from one to three months as required.

This method requires no extraordinary precautions and presents but two remote possibilities for error. The first, puncturing the rectal wall while injecting, is practically impossible providing a seven-eights inch needle is employed and the needle is inserted at the edge of the circumanal pigmented area. The second precaution is only required in males where the urethra can be avoided by not injecting along the mid-line anterior to the commissure. It is doubtful whether the injection of normal saline solution would cause any damage to these structures even though any one of these two errors was committed. There have been no complications following the use of the method and abscess formation has not occurred.

No attempt is offered to explain how this treatment achieves its results although a non-specific mechanism is suggested.

SUMMARY

The technique of the local injection of sterile normal saline solution is presented for the relief of pruritus ani. This procedure is outlined especially for the benefit of the general practioner. No particular instruments, special solutions nor a detailed knowledge of the anatomy are required to secure therapeutic success. The technique is a simple office procedure which is painless and does not incapacite or inconvenience the patient.

A report of thirty-one cases is included.

REFERENCES

1. Schatz, W. J.: *Penna. M. J.*, Aug., 1934.
2. Goldbacher, L.: Rectal Diseases in Office Practice, p. 356, 1935.
3. Pennington, J. R.: Rectum, Anus and Pelvic Colon, p. 247, 1923.

Annual Abstracts of Protologic Literature

(May, 1934-May, 1935) By CLEMENT L. MARTIN, M.D., Chicago, Illinois

The complete bibliography from which these Abstracts were made will be published in full in the Transactions of the American Proctologic Society, 1935.

COLITIS

Amebic Colitis (see separate heading).
Chronic Ulcerative Colitis (see separate heading).
Irradiation Colitis (see separate heading).
Simple "Colitis," Mucous Colitis (Colopathy, spastic, hypertonic; hyperkenetic; allergic; vagatonic, atonic; reflex, functional; irritable colon, etc.).

Hurst makes the point that the diagnosis "mucous colitis" is often made when the real trouble is achylia gastrica, rectal constipation (dyschezia) abuse of cathartics or enemas and colon irrigations. He urges the use of Ewald's term mucomembranous colic, to separate one entity from true colon inflammation. A congenitally small anus, which he regards as a not uncommon cause of constipation, acquired anal stricture following hemorrhoidectomy, anusitis with or without hemorrhoids, or fissure may be an important factor in some cases. He uses medical diathermy for the relief of these.

Although it was probably known even before the days of doctors that "one man's food was another man's poison," and medicine has for years been familiar with idiosyncrasies to certain foods, more exact information is being acquired. Food allergy is being studied; although to some it may mean anything from the gastro-intestinal stasis and other disturbances occurring in psychopathic states to the intestinal and general toxemia of acute appendicitis, its all-inclusive use is not the fault of the real contributors to the subject. Vaughn regards allergy as a foreign protein reaction, with the underlying mechanism responsible "not so much a pathologic condition as a pathologic exaggeration of a normal physiological response." He points out that the tendency is toward loss of hypersensitiveness and thus recovery and that the average period of necessary avoidance of the offending food is four and a half years. As the knowledge of the protein chemistry concerned in digestive processes advances, food allergy may occupy a less uncertain basis than it now has. Last year in an exhibit on nutrition sponsored by Alvarez, Fitz and Jeans in the A. M. A. Scientific Exhibit a pamphlet was given out containing this statement. "The following foods in the order named were found most often to be the cause of digestive trouble: cabbage, apples, tomato, milk, chocolate, onion, lettuce, coffee, strawberries, eggs, meat, cucumber, sweets, fats, radishes, cheese, cauliflower, peppers, prunes, oranges and salmon. Food allergy is not considered in this list."

Vaughn states the list contains the commonest allergic foods. Because of difficulties in the skin test, *i.e.*, not more than 50% of skin sensitization tests give positive results with the food protein responsible for hypersensitiveness, groups of proteins given as a single test and elimination diets are used.

Krouse thinks a study of colon form and function important considerations in getting a clear idea of the trouble with the patients having simple "colitis"; he favors the term colopathy and limits colitis as Bargen does to definite colon inflammation. He states "the limited benefit resulting from correction of local abdominal and rectal lesions, intestinal flora and allergic intolerances must be admitted. In studying these conditions, the bowel form (length, loopings, decompensation) as well as hypertonia and atonia must be considered."

Eggleston emphasizes that the trouble is not primarily intestinal in origin, but that an anxiety state, in a person having an unstable or poorly co-ordinated nervous system, is primarily the cause of the colon dysfunction; also "that there are those who consider the hypertonic colon an allergic reaction because of its similarity to asthma. Until more is known of the subject of allergy, I think it best to consider it a vagotonic manifestation . . . and that the real cure comes as a result of education rather than some method which may temporarily relieve the constipation."

With due regard for the careful work some students of the condition are doing, the helpful suggestions for further study and for treatment which such work gives, as well as a respectful acknowledgement of the insight indicated in Eggleston's opinion just quoted, and in *Bastedo's* clinic, one can readily see from the foregoing that we can not offer much under the heading of "recent progress in colopathy."

CONSTIPATION

Beck in "The Management of Chronic Spastic Constipation" gives a general review of the subject. Chronic constipation progresses usually through three stages: atonic, catarrhal, and spastic. The latter is perhaps the commonest variety for which the physician is consulted. He lists the causes as constitutional, eating habits, diet, cathartics, neglect, diseases, e.g. of stomach, liver, intestines, anaemia, functional neuroses, and others. Treatment is given in detail. *Spencer* does not hesitate to start his paper with "Constipation is a symptom not a disease," trite though it may be. He considers the subject from the standpoint of the physiology and the pathological physiology concerned. Associated causes may be failure to respond regularly to the urge to defecation, dietary factors, cathartic abuse, sedentary habits, obstruction from bands, and adhesions usually causing right sided stasis; stasis from emotional states, irritating food residues, lead, tobacco, caffein, organic diseases of the lumbar cord and inflamed mucosa, however caused.

In his discussion of spastic constipation he does not support the classification atonic and hypertonic (spastic). "There is little or no evidence for atonic constipation." He describes the spastic type as a definite entity and cites *Buckstein's* grouping based on stasis proximal to some par-

ticular sphincter or in a definite segment of bowel. A very rational therapy is described.

CONGENITAL ANOMALIES

Kantor describes a logical procedure to assist in locating the blind end of the rectum in imperforate anus. After a colostomy has been functioning satisfactorily, a catheter on a catheter guide is passed through the colostomy stoma into the lower segment and after incision of the anal depression a finger is passed upward to palpate the end of the catheter.

Rhodes reports a case and discusses the method of caring for this condition.

A colostomy in an infant is less satisfactory than in older patients; even so in case of complete atresia it offers the infant a better chance for its life than blind exploration to locate the rectum if the blind end is much separated from the anus.

Kantor records his study of 2000 cases of anomalies of the colon. He classifies them as follows: Redundancy, Non-rotation, Hypodescent, Hyperdescent, Hypofixation and Hyperfixation. Unless obstruction occurs these should generally be treated conservatively. Symptomatic treatment is all that is usually required.

Gardner and Hart state that a knowledge of normal intestinal rotation is important to an understanding of the possible abnormalities. They report 2 cases of volvulus of the entire mesentery giving symptoms of duodenal obstruction and review 103 reported cases.

SECTION IX—*Book Reviews*

(This section is open to contributions from any medical reader, whether or not a member of the Editorial Council).

Medical Treatment of Gall Bladder Disease, by Martin E. Rehfuss, M. D., Clinical Professor of Medicine and Guy M. Nelson, M.D., Instructor of Medicine, both of Jefferson Medical College, Philadelphia, Octavo 467 pages, Illustrated. Published late in 1935 by W. B. Saunders Company, Philadelphia. Cloth $5.50 net.

NO type of book so appeals to the practitioner as does one concerned with *treatment*. In the book discussed, the Authors have presented *in extenso* those forms of management which they have found most useful in the care of patients affected with "gall bladder" disease. What they exhibit may not be wholly acceptable to other authorities in this kind of affection, but at least a definite plan of treatment is presented. In a field which has been so chaotic, such is a major achievement. However, the Authors have discussed much more than therapy. What perhaps, is of as great value, is that they have furnished excellent summaries of etiology, pathology, physiology and, though it may not be directly germane to the subject of treatment, they have gone deeply into methods and results of diagnostic procedure. Their own work—a very considerable contribution to our knowledge of liver, gall bladder and duct disease, etiology and pathology—and that of others, has been set forth in such detail as to comprise a veritable encyclopaedia upon the modern knowledge of the subject considered. Certainly, one who reads this book by Rehfuss and Nelson cannot fail, instinctively, to contrast it with texts—as those of Rolleston—which, for some thirty years, have been regarded as "standard." This contrast is, in all ways, educational, since this latest volume makes a valiant attempt to premise all therapy on sound facts, not clinical opinions by so-called "authorities" or compilations of more or less questionable data from many non-related sources.

Today's idea of basing treatment upon established facts cannot be commended too strongly; it may mean a less flowing style of manuscript, a book not capable of being read "in an evening," a shorter list of "remedies" and a feeling that there is much yet to learn about the subject, but it eliminates a vast deal of guessing, glibness and cocksureness, and confines management along paths which are well-trod and give promise of leading somewhere, even though that "somewhere" may be not a journey's end.

By chapters which include complete summaries of accepted knowledge of The Problem, Gall Bladder Anatomy, Clinical History, Methods of Examination, etc. (24 in all) the Authors pave the way for sections discussing management by diet, medicinal agents, duodenal tube "drainage," spa regime, surgery. Each chapter is a complete exposition of its topic and, what is more, to the reader, a definite, reasoned plan submitted in accordance with what the writers have found useful in day-by-day clinical and private practice. This sort of thing is what makes the volume invaluable to the general—and the special, too—practitioner; so invaluable that he cannot afford not to have the book right at hand for daily guidance. We venture to prophesy that not alone will the dietetic tables and prescriptions of Rehfuss and Nelson find their way into "patients' orders" of inumerable practitioners but that, as a result of the issuance of this book, more rational management of "gall bladder" disease will be observed, much to the distress of the manufacturers of the all-too-numerous nostrums which now flood the market as "specifics."

While one may disagree as to whether diets largely should be carbohydrate, so that the diseased "gall bladder" may experience physiologic rest, or preponderately fatty (excluding the denser meat fats) and thus stimulate emptying of the viscus, nevertheless, he will agree that the Authors' discussions and their dietetic lists furnish adequate guides for the selection of menus which prove sufficiently varied for the average patient. It would appear that when the "gall bladder" disease is acute or sub-acute, exhibition of diets which largely consist of carbohydrates will prove most helpful, whereas the patient who harbors a chronic affection will be benefited most by fat-containing diets which aid in preventing gall bladder retention. In each type of ailment, all authorities agree that the

minimum of cholesterin-containing or producing foods is demanded.

Endorsement of spa regimens, common to Continental physicians, suggests that the training of the Senior Author definitely has been influenced by the French clinicians. It is perhaps, unfortunate that physicians of the United States have failed to appreciate the advantages to "gall bladder" patients of the several excellent "Springs" here available. What may be the significance upon pathology of the biliary tract, of drinking medicated waters is open to question, but, amply, it has been demonstrated that, at the spas, the regulation of diet, exercise, rest and sleep, combined with changes of scene and freedom from the worries and responsibilities of business, home or society, distinctly are helpful to the "bilious" subject. Here and abroad, only the too-inclusive claims respecting the potency of the various waters, and the air of commercialism and semi-charletanism prevalent at spas have mitigated against the wide professional acceptance of resorts catering to balneo-therapy. It seems quite probable, though, that if the pitch of American business and social activity continues high, the day is not far distant when, under really honest and capable professional guidance, our spas and their regimens again will be called upon to take care of the ever-increasing army of "liverish" citizens. Perhaps Drs. Rehfuss and Nelson have sounded the warning note in their excellent treatise.

Very unfortunate, indeed, is it that a book of such eminent qualities as this should be so woefully mistitled.

It has taken full twenty years for investigators and clinicians to establish that "gall bladder" disease is but part of an extensive, often progressing, lesion involving common-duct, gall bladder, with its cystic duct, hepatic ducts, their ramifications so far as to include duct "capillaries" and the very substance of the liver itself. Even more to the point is it, that the Authors' tremendous and inclusive amount of investigative effort (particularly that of the Senior), all of which is exhibited in detail in their book, so very definitely proves that when the gall bladder is diseased, that affection is but *part* of lesions of similar kind, though they may vary in degree, of the other segments of the bile producing and excreting apparatus. This makes one truly astonished at the volume's limiting title. Further, as one reads this valuable work, certainly, he is impressed that the advocated treatment programs constitute far more than one is accustomed to call "medical."

Would it not be an indication of now-known pathology, physiology, chemistry, metabolism and nutrition, dietetics, physiotherapy and the use of medicinal agents, as well as a needed, constant warning against dangerous, outmoded, limited clinical thinking, were this important volume titled, "Non-Surgical Management of Biliary Tract Disease." The reviewer thinks so. He believes that, as anyone studies the altogether admirable plans of treatment detailed, the conviction most strongly grows that "gall bladder" and "medicine" constitute but small portions, respectively, of disease discussed and therapeutic effort applied. It is our hope that the first edition of this work very rapidly is sold so that, with the issuance of another edition, a title is given which correctly conveys what really is to be treated and broadens the conceptions of suggested therapeutic aids. Apart from this being just to the reputations, the investigative studies and the clinical experience of the Authors, such adjustment of title is called for, so that constantly there may be carried to our profession the knowledge that "gall bladder" disease is a mis-nomer. One's conception should include a set of clinical syndromes frequently, but not always, associated with disease or improper chemical or physiological function of the gall bladder. Unless, the clinician grasps this essential distinction, his horizon is limited with respect both existing and possible subsequent tissue-faults, in regards the histopathogenic meaning of complications and, perforce, intelligent exhibition of diets, drugs, exercise. Further, biliary tract pathology—frequently not significantly due to that present in the gall bladder—so markedly disturbs general systemic welfare and brings digestive lamentations from the oesophagus, stomach, duodenum and the bowels (we but mention the glycosuria associated with secondary pancreatic dysfunction that we may call attention to the many, long-lived "diabetics" in every community who uselessly take insulin and "special diets"!)—lamentations not silenced by cholecystectomy or by years of "duodenal tube drainage of the gall bladder," that the need for a view broader than that focused upon the too-often maligned or attacked gall bladder, has become imperative. Too few years since, removal of the "chronic appendix" was esteemed a panacea for a multitude of dyspepic discomforts and storms, most of which persisted or reappeared soon after appendicectomy. This book by Drs. Rehfuss and Nelson demonstrates emphatically why, with his eye on the gall bladder alone, when the surgeon performed cholecystectomy (or cholecystostomy; the storm still rages as to which is the better procedure; as routine operations, both are gambles) the internist later treated the "bilious dyspepsia"—the digestive disturbance which, in large part, from its beginning, depended upon biliary tract disease, not pathology or upsets in excretory, chemical or physiologic function of the gall bladder alone.

This book by Rehfuss and Nelson, though it be mistitled, follows the admirable modern trend of issuing authoritative monographs upon special topics, instead of printing huge volumes which rarely are more than out-dated compilations from the literature, made by one or a group of questionably qualified, so-called "authors." Just as the recently published monograph of Eusterman, Judd and their affilliates supplied our profession with worth-while discussions of ailments of the Stomach and the Duodenum, so this latest Saunders' effort aims at rational covering of the "gall bladder" (more accurately, biliary tract) field. Such plan of publishing appeals strongly to the reviewer. He feels that the day is past when, except in books of the "quiz-compend" type, physicians will load their shelves with expensive "systems" or thick, heavy, difficulty handled, single volumes, purporting to cover all subjects and oft, indeed, compiled (and all too often actually *written*) by medical, literary "hacks" or the young assistants of important, but alas, too busy for actual book-writing, clinicians. The trend towards the publishing, at fair prices, of single books, filled with down-to-date matter, actually submitted by men who are recognized authorities, we believe, means a revival of activity to the medical book-printers and a recreation of physicians' interest in book owning and

reading. But the books which are printed must be authoritative, must be well arranged as to text and illustrations and above all, must be sold at fair prices.

In issuing Drs. Rehfuss' and Nelson's book, the Saunders' Company has demonstrated what can be done along these lines. The volume is of size easily handled while being read, is bound substantially, has strong white paper which well takes a type-font restful to the eyes, is carefully indexed and yet, with all these advantages, is sold at a price which physicians can pay.

Frank Smithies.

SECTION XI—*Societies, Programs and Proceedings*

Program of the 39th Annual Session of the American Gastro-Enterological Association

MAY 4TH AND 5TH, 1936

ATLANTIC CITY, NEW JERSEY

MONDAY, MAY 4TH, 1936

MORNING SESSION, 9:30 A. M.

MEMORIAL ADDRESSES

Dr. John Bryant, Dr. Lafayette B. Mendel.

PRESIDENTIAL ADDRESS

Dr. Howard F. Shattuck, New York, New York.

"Hypoglycemia—A Clinical Survey of Four Hundred Cases Having This Common Finding." Dr. Lay Martin, Baltimore, Md.

"Thoracic Stomach and Diaphragmatic Hernia." Dr. Leon Bloch, Dr. A. M. Serby (by invitation), Dr. Samuel Salinger (by invitation), Chicago, Illinois.

"A Consideration of Some of the Newer Methods for the Treatment of Peptic Ulcer." Dr. Andrew B. Rivers, Rochester, Minn.

THE ALVAREZ LECTURE

Founded in 1929 by Dr. Frank Smithies, Chicago.

"The Digestive Tract in Anemia." Dr. George R. Minot, Boston, Mass.

Adjournment for Luncheon.

2:30 P. M.

"Miscellaneous Observations on Intubation of the Small Intestine." Dr. T. Grier Miller, Dr. W. Osler Abbott, Dr. Walter G. Karr (by invitation), Philadelphia, Penn.

"Regional Ileitis." Dr. A. A. Berg, New York, N. Y.

"The Components of Gastric Secretion." Dr. Franklin Hollander, New York, N. Y. (by invitation).

"Gastric Secretory Behavior in Chronic Gastritis." Dr. H. L. Bockus, Dr. J. F. Monaghan (by invitation), Dr. Karl Kornbloom (by invitation), Philadelphia, Penna., Dr. George R. Moffett (by invitation), Harrisburg, Penn.

EXECUTIVE SESSION

(For Fellows of the Association only).

ANNUAL DINNER, 7:30 P. M.

GUEST OF HONOR

Dr. William Mather Lewis, President Lafayette College, Easton, Penn.

"The Cultural Background of the Professional Man in Medicine."

TUESDAY, MAY 5TH, 1936

MORNING SESSION, 9:00 A. M.

"Further Experimental Studies on the Etiology of Ulcerative Colitis: The Possible Virus Factor." Dr. Moses Paulson, Baltimore, Md.

"The Diagnostic Significance of Anti-Dysentery Bacteriophage." Dr. T. T. Mackie, New York, N. Y.

"Symposium on the Pancreas."

Physiological Aspects: Dr. A. C. Ivy, Chicago, Ill.

Pathological Aspects: Dr. William G. MacCallum, Baltimore, Md.

Medical Aspects: Dr. Thomas R. Brown, Baltimore, Md.

Surgical Aspects: Dr. Daniel F. Jones, Boston, Mass.

"Report of Special Committee on Enzymes." Dr. A. H. Aaron, Chairman, Buffalo, N. Y.

Adjournment for Luncheon.

2:00 P. M.

"Cholesterol Metabolism in Jaundice." Dr. S. Allen Wilkinson, Boston, Mass.

"Biliary Stasis." Dr. Carl H. Greene, Dr. J. Russell Twiss, Brooklyn, N. Y.

"Chronic Hepatitis with Jaundice (Biliary Cirrhosis)." Dr. James F. Weir, Dr. Albert M. Snell, Rochester, Minn.

"The Prognosis of Acute Hepatic Insufficiency." Dr. Chester Jones, Boston, Mass.

"Macrocytic Anemia in Diseases of the Liver." Dr. David H. Rosenberg, Chicago, Illinois.

"Specific Food Sensitiveness." Dr. Walter Alvarez, Rochester, Minn.

(Asociación Mexicana de Gastro-enterologia)

AT Mexico City, Republic of Mexico, on July 17, 1935, there was organized the "Asociación Mexicana de Gastro-enterologia."

Dr. Abraham Ayala Gonzalez, Mexico City, was elected President.

The Association's main purposes, as set forth in its Articles of Incorporation and its Constitution are:

1. To bring together physicians specializing in this branch of medicine.
2. To encourage and to broaden the study of Gastro-enterology in Mexico.
3. To facilitate, in Mexico and abroad, interchange of specialized studies in this field of medicine.
4. To initiate and further research studies in Gastro-enterology.
5. To establish, publish and issue an official periodical for the Association, titled "The Mexican Review of Gastro-enterology."*

The official address of the organization is: "Asociacion Mexicana de Gastro-enterologia," Marsella No. 47, Mexico City. Communications for the present, should be addressed directly to Dr. Abraham Ayala Gonzalez, President.

*The periodical, nationally, is titled, "Revista de Gastro-enterologia." Volume I, No. 2, dated November-December, 1935, recently has been received. Editor.

SECTION XII—*"The Clinic"*

Gastro-Duodenal Hemorrhage of Unknown Origin: A Case Report

By

CHARLES D. ENFIELD, M.D.
LOUISVILLE, KENTUCKY

WE have long been familiar with the type of patient, whose first gastro-intestinal symptom is a massive hemorrhage; who was prior to the moment of bleeding able to eat anything without discomfort; who experienced no typical chemical discomfort; and who had in fact considered himself to be in excellent health until floored by the hemorrhage. These patients have frequently shown no abnormality whatever on X-ray examination and are, as a rule, put on ulcer management purely on the clinical assumption that the bleeding must have come from an ulcer. Not infrequently these patients go on to complete recovery, never have ulcer symptoms, and never have another hemorrhage; or they may have repeated hemorrhages without ulcer symptoms.

We have also long been familiar with the type of individual, who, under nervous strain, develops typical ulcer symptoms with hyperacidity, but who fails on careful X-ray examination to show any ulcer deformity. These patients many of us have classed as instances of gastro-duodenal expression of apprehension, nervous fatigue and worry, and they are usually relieved by an improvement in their business or domestic situation, a trip abroad, or in fact anything that relieves the nervous tension. They are generally high strung, energetic and of greater than average intelligence. Many of them are doctors and I am sure all radiologists have had the experience of having a friend in the profession present himself with a self-made diagnosis of ulcer or occasionally gastric cancer only to find on repeated examination no evidence of any lesion whatever.

Submitted December 9, 1935.

This case history suggests that perhaps these two groups—the one with hemorrhage but with no symptoms and no duodenal deformity and the other with typical ulcer symptoms but without hemorrhage and likewise no duodenal deformity, may occasionally combine into an undoubtedly much smaller group, which may evidence not only a typical clinical picture plus hemorrhage, but also a typical Roentgen appearance.

It has appeared to the careful and well trained radiologist that the diagnosis of duodenal ulcer with almost mathematical certainty ought to be chiefly a matter of expending sufficient time, effort and skill in demonstrating the niche. This procedure is more difficult in certain types of patients, easier in others. For many years a small percentage, perhaps up to thirty-five per cent, of niches have been demonstrated without special apparatus or technique. The demonstration of a niche can be greatly facilitated by the use of various forms of special apparatus, mostly hinging about compression devices, and with their wider use the percentage of niches demonstrated has increased materially. It is felt by the majority of radiologists that where a niche can be demonstrated, there should be no practical doubt as to the existence of an ulcer, and, conversely, it should be possible to demonstrate a niche, where an ulcer exists, in a very high percentage of cases.

CASE REPORT

The patient, a white, male physician, whose case I wish to report, had occasional attacks of abdominal distress as a child, more severe than the ordinary attacks of colic. As a young man, these attacks occurred at intervals of a year and a half or two years, sometimes required morphine, and were invariably relieved by twenty-four hour

abstention from food, and were usually accompanied by vomiting.

In 1922, at the age of thirty-six, he began to have definite, typical ulcer symptoms with attacks in the spring and occasionally in the fall, lasting three or four weeks. He was relieved by almost anything *remotely* approaching Sippy management. He was likewise relieved by a change in environment, a rest, a trip, sometimes by belladonna. During the nine years in which the symptoms persisted he worked out a thoroughly unorthodox method of management, which, however, left him in a fair degree of comfort and able to attend to his work practically without interruption. He was profoundly aware that certain foods, such as pork, all members of the bean family, highly seasoned sauces, pickled or smoked meats or fish were apt to disturb him acutely. He found he was almost never disturbed by lobster, shrimps, and many other articles of diet commonly interdicted for ulcer patients. His lesion seemed to have no tendency to perforate or to bleed and for several years he was firmly convinced that a reasonably intelligent individual could get along quite comfortably with a duodenal ulcer, if he humored it a little.

During these years the patient was examined by several radiologists, more than one of national repute, and in each instance a typical duodenal deformity was demonstrated with ease and constancy. The last two or three examinations showed a definite niche or ulcer crater penetrating posteriorly in the direction of the pancreas. Since this niche was demonstrated on not one but on a considerable series of films and not at one examination but at least on three occasions separated by several months, there was no doubt in the mind of the patient or of his medical advisors that he did in fact have a chronic penetrating duodenal ulcer.

During this period several gastric analyses were made, all of which showed abnormally high acids and most of which showed chemical blood.

About nine years after the onset of definite symptoms, the patient suffered without warning a massive hemorrhage, which almost proved fatal, and for which an emergency laparotomy was performed. Transfusions were given before and after operation. Neither the surgeon nor the internist chiefly concerned were at all enthusiastic about operating during gastric or duodenal hemorrhage but the failure of medical measures to control the hemorrhage with a hemoglobin estimated at twenty-three per cent of normal convinced both of the desirability of operating as an emergency procedure. No attempt was made to do anything other than find and close the bleeding point, and there appears to have been some question as to whether this was successfully accomplished since the patient bled again five days later.

Symptoms recurred within a few weeks and were at first confined to typical chemical discomfort relieved by alkalies. However, other hemorrhages ensued and, as there appeared to be some tendency to obstruction or at least some delay in emptying the stomach, a gastro-enterostomy was performed by another surgeon.

Symptoms still persisted and hemorrhages continued. Approximately two years after the first hemorrhage and emergency surgery, and approximately a year after the gastro-enterostomy, the patient went to the operating table a third time and the stomach below the gastro-enterostomy was removed together with the first part of the duodenum. The gross specimen was found to show no ulcer, no scars, and in fact to present the appearance of perfectly normal gastric and duodenal mucosa. The duodenum was not adherent to the pancreas. The specimen was submitted to a competent pathologist, who reported both the gross and microscopic appearance normal, and he was not more successful than the surgeon had been in finding evidence of ulcer, old or recent.

The complete failure to find any pathological explanation of the perfectly typical ulcer symptoms, extending over a period of eleven years, and accompanied by typical X-ray findings on numerous occasions, was a shock in more ways than one. The only possible explanation of the X-ray appearance in the light of the negative pathological findings seems to be that it was caused entirely by spasm, perhaps purely of functional nervous origin, or possibly due to superficial mucosal ulcerations, which healed promptly and without scarring. Naturally the X-ray examinations were made at times when symptoms were unusually pressing, and certainly the combination of circumstances here recorded must be so rare as not to discredit to any serious extent the accuracy of X-ray diagnosis of duodenal lesions. It should perhaps be emphasized that the X-ray examinations referred to were performed without special compression devices and in fact prior to the invention of most such devices now in use. There is in the writer's opinion little doubt that the compression device itself may under certain circumstances cause, in the normal duodenal bulb, an appearance closely simulating an ulcer crater.

Treatment of Chronic Ulcerative Colitis

Report On Five Cases

By

EMOR L. CARTWRIGHT, M.D.
FORT WAYNE, INDIANA

THIS devastating disease is assuming more serious proportions each year. While great strides in its treatment, have been made by Bargen and others, it is still true that the acute fulminating type may terminate fatally or, in the event of recovery, leave the patient with a permanently crippled colon. As stated by Bargen, the patient with chronic ulcerative colitis must be considered in the same light as a patient with pulmonary tuberculosis. The disease may be arrested, but there is the ever-present threat of recurrence.

Any remedy which aids in the control of this malady is worthy of being brought to the attention of the medical profession. We have found such a remedy in Alpha Naphco Jelly and liquid. While we believe that the Bargen serum is needed in the acute fulminating type, Alpha Naphco is an excellent remedy after the case has been brought under control. This remedy

Submitted December 9, 1935.

alone, however, will suffice to clear up cases of the ambulant type.

The following five case histories are reported from a clinical standpoint only. The clinical diagnosis in all was chronic ulcerative colitis. The progress of each case was followed through the proctoscope. In three of the cases a number of the usual remedies had been used by the referring physicians before I finally saw the patients.

CASE REPORTS

F. M., Male, 25 years old, January 29, 1935.

I saw this young man first in February, 1932, when he was bedfast with a fulminating type of chronic ulcerative colitis. At this time the Bargen serum was used which brought about a remission in the disease. Since that time he has had several recurrences. The last one occurred January 29, 1935, and he was put on Alpha Naphco liquid 25 gtts in hot water after meals and Alpha Naphco capsules four before each meal. This was the only treatment given and it very promptly brought about a remission. He was dismissed February 18, 1935.

A. I., Female, 50 years old, November 10, 1935.

History: Since June, 1933, she has been passing blood and mucus as soon as she gets up in the morning, having several such movements before noon. She usually has a bowel movement about noon. She has had no pain and no cramps. She has lost no weight, but she is somewhat weaker.

She had malaria thirty years ago here in Allen County, Indiana, but has had no other serious illness.

The referring physician stated that he had given her hypodermatic injections of emetine and a course of carbarsone by mouth.

Examination: Palpation of the abdomen revealed no tenderness and no tumor masses. The anal margin was negative. The anal canal was inflamed and bled easily. Proctoscopy revealed a boggy mucosa with minute ulcerations. A ten-inch sigmoidoscope was passed, and minute ulcerations were found in the sigmoid mucosa. The mucosa was spotted with blood flakes.

Treatment began November 10, 1934. She was put on Alpha Naphco capsules and liquid. She took two capsules before each meal and at bedtime, and 15 drops of the liquid every hour in hot water, ten doses daily. This was the only treatment she received and it was continued until she was well.

November 21st. Proctoscopy revealed blood and mucus in the rectum.

November 22nd. A warm stool was examined at St. Joseph's Hospital, and no amebae were found. The stool contained pus and blood.

November 24th. The capsules were increased to four, four times daily and the liquid to 25 drops every hour.

November 28th. Proctoscopy showed the mucosa healing. It was not so boggy and the bleeding was less.

December 5th. Proctoscopy showed the mucosa healing.

December 13th. Proctoscopy showed the mucosa to be practically normal and she was dismissed.

To date, (September 20, 1935), there has been no recurrence.

D. C. S., Male, 27 years old, April 12, 1935.

History: Patient had consulted the referring physician one year previous to the time I saw him. Various irrigating solutions had been used, and numerous intestinal antiseptics had been administered without any help. Bleeding from the rectum continued. He would pass blood immediately after getting up in the morning, have a bowel movement, and then pass more blood.

His previous history was negative. He has spent his entire life in Indiana excepting three years spent in Boston.

Examination: Inspection and palpation of the perianal region were negative. The anal canal was free from any pathology.

Proctoscopy showed beginning hemorrhoids in the lower rectum. The mucosa was boggy and bled easily. There were multiple bleeding areas with tiny ulcerations in the rectum and in the sigmoid. The picture was typical of chronic ulcerative colitis.

Treatment: He was put on a bland diet. On April 17, 1935, he was started on Alpha Naphco liquid 15 gtts every hour in hot water and Alpha Naphco capsules, two before each meal.

April 22nd. Proctoscopy showed the mucosa to be looking better. Patient stated that he has not passed any blood for two days.

May 1st. He had noticed recurrence of blood, so the dosage of the Alpha Naphco liquid was doubled.

May 8th. He was passing no blood and he continued to improve until May 24th when sigmoidoscopy showed a recurrence of the disease all along, with punctate ulcers. Alpha Naphco liquid and capsules were continued.

May 27th. He was much improved. He was told to discontinue raw cow's milk and to use instead evaporated milk.

June 3rd. The mucosa had healed, and he was passing no blood. Dismissed.

To date, October 14, 1935, there has been no recurrence.

S. G., Female, 62 years old, September 24, 1935.

History: For the past two months she has had rectal bleeding. Passes blood the first thing in the morning and then some at stool a little later. Previous to this she was well excepting that she would tire easily. A year ago a doctor told her she was anemic. She has always been constipated.

Examination: Abdomen negative. Digital examination of the anus is negative. Anoscopy shows bloody mucus in ampulla. Proctoscopy shows a boggy mucosa with ulcerations. Mucosa bleeds easily when touched. No tumor found.

Treatment: She was started out on brewers yeast, bismuth subnitrate, mineral oil, and cod liver oil.

October 8th. All medicine was discontinued and she was put on Alpha Naphco liquid 20 gtts in hot water every hour. She could not take capsules saying she positively could not swallow them. As she was constipated, sodium phosphate was prescribed.

October 22nd. Cod liver oil was again started.

October 29th. She was feeling much better. Passing less blood.

November 12th. (No Alpha Naphco on hand). She was put on Karicin which she took for about four weeks. It was discontinued later.

December 17th. She was started on Alpha Naphco liquid 30 gtts in hot water every hour, ten doses daily. This medication was continued during the winter and in February, 1935, she was all right.

In June, 1935, she had a recurrence of the rectal bleeding. She was put on reduced iron tablets. Alpha Naphco liquid was started again and was continued during the summer.

August 7th. Her teeth were X-rayed and found to be normal.

September 4th. Proctoscopy showed the mucosa to be normal and she was dismissed.

October 31st. An X-ray following a barium enema was negative excepting for the evidences of a healed colitis. On account of her age the Alpha Naphco liquid will be given intermittently with the hope that it will prevent any recurrence.

C. S. A., Male, 28 years old, April 17, 1935.

History: In November, 1934, he noticed a little blood after a bowel movement. He has had no pain but an uncomfortable feeling in the abdomen. He has lost neither weight nor strength.

His home was in Mississippi until July, 1929, when he moved North. He had the usual childhood diseases, nothing else, and no operations. He never had malaria nor any dysentery. The referring physician states that he has used anti-amebic treatment (emetine) and also some of the arsenic preparations. Rectal irrigations were used over a long period.

Examination: Abdomen negative. Inspection and palpation of the perianal region and anus were negative. Proctoscopy showed an edematous and redundant mucosa, containing many tiny ulcerations. The rectum contained some bloody mucus. Sigmoidoscopy at six inches showed a normal mucosa.

On April 20, 1935, warm stage examination showed nothing but red cells.

Treatment: He was started on Alpha Naphco liquid 15 gtts every hour in hot water, ten doses daily, and Alpha Naphco capsules two before each meal.

May 1st. There has been no improvement.

May 4th. Patient states that he is feeling a little better. Mucosa looks a little better.

May 13th. Not so good. There was free blood in the rectum.

May 15th. Mucosa a little better.

May 22nd. A little better.

May 27th. No improvement. To discontinue pasteurized milk.

May 31st. Increase Alpha Naphco capsules to three, four times a day.

June 20th. Has not passed any blood for two weeks.

June 27th. Some blood flakes in the rectum.

July 2nd. More blood in the rectum, but he is feeling fine. He is leaving the city for three weeks on a vacation. I gave him enough Alpha Naphco liquid and capsules to last during this period.

July 23rd. Returned from his vacation feeling fine.

July 30th. Mucosa is boggy but he passes no blood.

August 6th. Mucosa looks fine.

August 13th. Proctoscopy shows everything to be normal. Dismissed.

The experiences of others would indicate that respiratory infections are the greatest contributing cause of recurrences in chronic ulcerative colitis. With this in mind patients should be very careful not to contract colds. Their resistance should be kept up to par by eating abundantly of wholesome foods, and taking cod liver oil, during the winter months especially. While diet does not apparently play a very great role in the treatment of the disease, still I think it is wise to refrain from asking a sick colon to handle the residue from the leafy green vegetables.

ABSTRACTS

CLINICAL MEDICINE

F. R. BERNHARDT.

What is the Significance of the Invading of Stomach Contents into the Bile Ducts Following Anastomosis Especially Cholecocho-duodenostomies? Archiv. f. Klin. Chirur., Vol. 180, Sept. 21, 1934.

An exhaustive report is given of 22 cases where anastomosis was performed between the bile ducts and the adjacent organs with careful follow-up histories, roentgen examination included. This surgical procedure being recently undertaken more frequently, evolves the so-important question of ascending infection from the stomach or bowels. The answer is not uniformly affirmative. The Author collected, however, a certain number of cases where such infection has not occurred. It must be cited, however, that passing of duodenal content into the bile ducts is not always harmless and often is followed by damaging effects upon the mucosa of the bile ducts. The prevalence of acids are often playing a decisive role in that for instance in cases of decreased HCl secretion the administration of HCl and pepsin may counteract ascending infections with comparative certainty.

Entrance of the barium meal into the bile ducts was visualized in one case where the hepaticus was anastomosed to the stomach. In three cases of cholecystogastrostomies it penetrated once, in six cases of cholecystoduodenostomies it invaded twice and in 15 cases of choledocho-duodenostomies it gained access eight times into the bile ducts. In the latter cases concommitent attacks of cholangitic processes were observed. Possibly a dilatation of the smallest ducts was responsible for such complications. It is noteworthy that where barium did not invade the bile ducts cholangitis also was absent. Untoward results are often due to faulty technic such as too narrow anastomosis. In these cases a stenosis may be responsible for the complaints which are similar to those of common duct stones. Sometimes the retroduodenal portion of the common duct shows stasis and thus may give rise to secondary ascending infections. To overcome this, it is advisable to perform the anastomosis at the lowest point of the choledochus, an advantage resulting in diminished traction upon the duodenum.

Such operations ought to be considered as major surgical measures. Although often life saving they are not always harmless. Consequently indications must be taken very judiciously. Complete stenosis of the common duct with a functionless gall bladder is one of such indications. Other processes obstructing the flow of bile within the papilla also belong here. Another large group consists of lesions involving the pancreas, *i.c.* induration of the head, tumors, widespread adhesions obstructing thus a satisfactory flow of bile, etc. In such instances the choledochoduodenostomies are especially the operation of choice. Incidents are mentioned where the post-operative course remained satisfactory 18 years after such operation. In most of cases complete obliteration of the common duct was found. The gall bladder had been removed previously because of stones. Anastomosis was performed between the duodenum and the common duct resulting in stormy post-operative courses, manifested by severe cholangitis. In these cases the barium swiftly invaded the smaller bile ducts and almost invariably a shadow was seen in the retro-duodenal portion of the common duct.

Choledocho-duodenostomies should be performed in the appropriate cases with a most meticulous technic. Because of the possible complications, however, the indications for such procedures must be cautiously weighed.

M. E. Gabor, Milwaukee.

H. KALK.

Hereditary Factors in Lesions of the Gastro-intestinal Canal. Deut. Med. Woch., No. 39, Sept. 20, 1934.

A short and interesting survey is given about inheriting anomalies, constitutional types and finally diseases of

the gastro-intestinal tract. To ulcer disease is devoted a great deal of attention. "Ulcer Families" are described where the occurrence of ulcers could be traced to the second or third generation with almost identical complications such as hemorrhage and perforation. The contention that such stomachs are all afflicted with a lowered resistance, a so-called "Minderwertigkeit" is still a muted question. Malignancies of the stomach may also be inherited revealing sometimes identical predilection of invaded areas. Gastritis also may be found as revealing hereditary tendencies, manifested by achylias and pernicious anemias. The haemolytic jaundice described by the French as Familial Cholemias and by the Germans as Constitutional Hyper-bilirubinemia is well known. With regard to Cholecystopathias one can say that the stronger the hereditary tendency the sooner we may expect stone formation, inflammations or other derangements of the bile ducts.

M. E. Gabor, Milwaukee.

BODMAN, FRANK, M.D.

The Psychologic Background of Colitis. Amer. Jour. Med. Sc., pp. 535, Oct., 1935.

The writer states that the bacterial cause of ulcerative colitis has not been convincingly proven and it has been overlooked that it constitutes a terminal stage in a colon which has been the seat of disorganizing dysfunction. Ulcerative colitis is incurable as gross organic changes have taken place in the mucosa of the bowel, in the myocardium and in the elastic tissue of the arteries.

Prevention of these terminal stages can be attained if the functional disorder is recognized in good time and as partly an expression of an emotional state.

The Author predicates that colonic dysfunction begins during breastfed infancy. The baby upon defecation experiences discomfort, cries for his mother or nurse; a call for help or attention and another conditioned reflex in infancy may be established by the emptying of the bowel when the child is frightened — by being handled by strangers or examined by physicians in a children's ward.

The next psychologic factor in the development of bowel function is that invoked in the training of the infant to a regular reflex. This is the first demand made by society—through the mother or nurse on the infant. If the response to the reflex is prompt and satisfactory it receives encouragement —that if it fails to respond displeasure may be exhibited by its guardian. It has discovered a new channel for exercising power.

Twelve cases are described which illustrate the various stages and degrees of functional and organic disorders of the colon. The family and personal histories of these cases are meticulously dealt with and the psychogenic factors emphasized both in the development and management of the disorder.

Allen Jones, Buffalo.

ROSEDALE, R. S.

Jejunal Diverticulosis. S. G. and O., Vol. 61, No. 2, pp. 223-228, Aug., 1935.

Multiple jejunal diverticulosis is a rare condition; the Author has been able to find 71 recorded cases to date. Jejunal diverticula are classified as congenital, or acquired. The congenital diverticula are made up of all the layers of the intestinal wall, while the acquired ones contain only a fraction of the layers of the intestinal wall.

The etiology of these diverticula is obscure. Increased intra-intestinal tension, embryologic incoordination, and weakness of the intestinal wall at the point of entry of the vessels are probably important factors in their formation. Butler has concluded from some experimental work that sclreosis of the terminal branches of the superior mesenteric artery and the resultant formation of "traction pockets" is also an important etiological factor in the formation of these diverticula.

Complications of jejunal diverticulosis do not occur frequently. They may contain enteroliths and cause partial intestinal obstruction, or they may become inflamed and cause vague abdominal pain.

The Author reports three cases in detail. Seven figures and a bibliography accompany the article.

Nelson M. Percy, Chicago.

BLOOMFIELD, ARTHUR L., M.D.

The Mechanism of Decrease of Gastric Secretion With Advancing Years. Amer. Jour. Med. Sc., p. 325, Sept., 1935.

Bloomfield and Keefer, in 1928, were the first to demonstrate the steady drop in acidity which takes place with advancing years. Polland and Bloomfield confirmed this finding through histamin tests on essentially normal people. Vanzant and her colleagues showed that men have a more highly acid gastric juice than women.

This work established:

1. There is a marked fall in the average gastric acidity of men with advancing years and the curve is a straight line.

2. The average gastric acidity of young women is distinctly lower than that of young men, but the fall with advancing years is very slight.

3. The average volume of secretion both men and of women falls markedly with advancing years and the curve is a straight line.

It was found that there was not a gradual fall in all people because even in the older age periods a number of individuals are found who preserve a maximal secretion.

The rapidly increasing incidence of anacidity with advancing years also seems out of accord with gradual drop in secretion of the whole population.

The writer says it was very difficult to accomplish followup studies over a period of 5 or more years, therefore, they had only 6 cases so examined. Many observations showed the amount of variation by tests at brief intervals to be slight. Rather slight differences in secretion volume and acidity were revealed in these cases though there was a lessening tendency. One must look elsewhere then, for the explanation of the general fact that gastric secretion decreases with advancing years. The answer lies in certain cases in which there is a very rapid deterioration of secretion. The Author cites 2 case abstracts of instances of this sort. One was the case of a 33 year old teamster with a penetrating type of lesser curvature gastric ulcer in 1927. His acidity was normal—he was re-examined in 1934 and no free HCl was found nor was the ulcer demonstrated by Roentgen ray. He had taken alcohol freely and returned with anorexia and had vomited for a year.

The second case was one of a penetrating ulcer with pyloric obstruction first seen in 1929. The patient was 57 years old. Histamine test showed free HCl 88—, total 98, height volume period 41 c.c. The ulcer was excised and gastroenterostomy was done. It showed a benign gastric ulcer. Histamine test, September 9, 1933, showed free HCl 0 and total 12; volume 17 c.c.

Discussion: The observations show there is no uniform steady decline of gastric secretion in all people with advancing years. The level of secretion remains essentially unchanged; there may be a slight increase or a rapid failure may occur and lead to anacidity.

Allen Jones, Buffalo.

NUTRITION

BAUMGARTNER, L.

Pituitary Basophilism and Hypertension. Yale Jour of Biology and Medicine, Vol. 7, p. 327, 1935.

Since Cushing's description of the clinical phenomena associated with basophilic adenoma of the pituitary, another approach to the study of the relation of the pituitary to clinical hypertensive disease has offered itself. Baumgartner selected 13 cases of hypertension in young individuals in whom arteriosclerotic and nephritic complications were minimal, and no other complicating disease was present. Detailed clinical study including blood chemistry, X-rays of sella and skeleton, visual field determinations and basal metabolism, was made, and the results compared with the data for the 23 cases of pituitary basophilism now in the litera-

ture. The features characteristic of pituitary basophilism occurred in relatively few of the hypertensives, but the method of selection would eliminate those with advanced signs of basophilism.

(a) Obesity occurred in the majority and the typical distribution of fat to trunk and face with marked sparing of the extremities was recognized in 4 of the 13. In 5 cases the sudden increase in weight comparable with Cushing's description had occurred.

(b) Skin and hirsutism. In none of the hypertensives did the characteristic purplish striae occur. Polytrichosis was noted in 3 of the 8 women.

(c) Sexual dystrophies did not occur, except for menstrual irregularities in 2 women.

(d) Osteoporosis was lacking although it was a decided feature in some cases of basophilic adenoma.

(e) Erythrocytosis with counts exceeding 5,000,000 occurred in 8 of the 13 cases.

(f) Pathologic examination in 2 hypertensives revealed a small basophilic adenoma of the anterior lobe, associated with infiltrations of the posterior lobe with basophilic cells in one case and a normal gland in the other.

Howard F. Root, Brookline, Mass.

SPIES, TOM D.

The Medical Treatment of Early Pellagra. J. A. M. A., 105:1028, Sept. 28, 1935.

The two main theories of the cause of pellagra are: First, that pellagra is caused by a bacterium. The second theory is that it is caused by the lack of a specific chemical substance present in food. Neither of these theories has experimental proof.

The mortality rate in pellagra is high. The treatment of the moderately severe case of pellagra should be generally known. The diet should be well balanced and contain 4000 calories. The patient should have adequate rest. In addition good brewer's yeast, wheat germ or liver extract should be given in large doses. Any of these agents are best given in doses of from 10 to 20 grams in a glass of iced milk or iced eggnog every three or four hours for a total of 75 to 100 grams daily. Parenteral injections of liver extract are very effective coupled with brewer's yeast or wheat germ given by mouth. The patient should be watched and guarded against relapses.

Francis D. Murphy, Milwaukee.

DRAKE, E. H., HAWKES, R. S., AND WARREN, MORTIMER.

An Epidemic of Trichinosis in Maine. J. A. M. A., 105:1340, Oct. 26, 1935.

The Authors discuss the first recorded epidemic of trichinosis in Maine and possibly the largest epidemic to be reported in the United States. Infection resulted from the eating of improperly cooked homemade pork sausages. The infected meat and the striated muscles of two fatal cases showed the trichinellae. Of seventy-one individuals known to have eaten the sausage, fifty-six revealed signs of infection. Twenty-six persons ill with probable trichinosis were given skin tests, twenty-four of these were positive. The technique of the intradermal test for trichinosis is discussed.

Francis D. Murphy, Milwaukee.

RALLI, ELAINE P., AND WATERHOUSE, ALICE.

Studies on the Effect of the Administration of Carotene and Vitamin A in Patients with Diabetes Mellitus.
II. The Effect of a Cod Liver Oil Concentrate on the Blood Carotene and Cholesterol.
The Diabetic Clinics of the Third (New York University) Medical Division, Bellevue Hospital, and the Department of Medicine, University and Bellevue Hospital Medical College, New York University. Jour. of The Amer. Diet. Assoc., pp. 110-114.

A previous study showed that when a group of diabetic and non-diabetic patients were fed carotene that there was a greater increase in the blood carotene in the diabetic patient than in that of the non-diabetic. Because of this fact a study was made on the effect of a cod liver oil concentrate on the blood carotene and cholesterol in twenty-seven diabetic patients. The ages of these patients varied from 22 to 68 years; 14 of which were over 45 years of age. Six of these fourteen had a severe case of diabetes and eight mild diabetes. Of the cases under 45 years of age, ten were severe diabetic and three mild. After a controlled period during which time observations were made on blood carotene and cholesterol, the patients were given cod liver oil in the form of a concentrate. Fasting samples of blood were taken at intervals and blood carotene and cholesterol were determined from these samples.

The results of this experiment shows that:

The blood carotene increased in seven cases, fell in seven, and showed no change in thirteen cases.

An increase in blood cholesterol was associated with an increase in blood carotene in twelve patients.

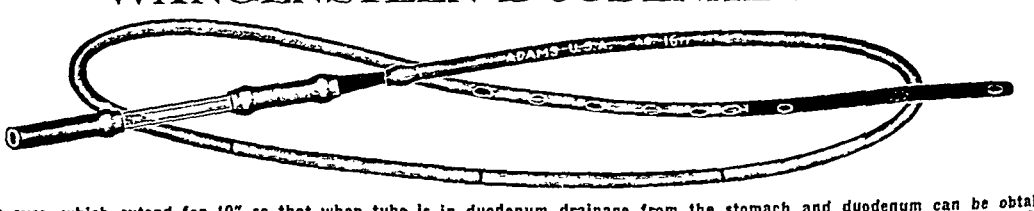
In fourteen cases the blood cholesterol changes were in the same direction as the blood carotene changes.

There seems to be no constant relationship between duration or severity of diabetes and the height of the blood carotene. The reaction of the patient to the concentrate was practically the same in the various groups. There were no complaints attributed to the high blood carotene.

These results indicate that the effect of the concentrate on the blood carotene is much less than the effect of carotene in oil. It is the opinion of the writers, that since there is a definite increase in blood carotene in diabetic patients following the administration of carotene *per se*, it might be wiser to use Vitamin A as such in these patients until the clinical significance of an increase in blood carotene has been established.

Clifford J. Barborka, Chicago.

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ROENTGENOLOGY

KIRKLIN, B. R., AND BLAKE, THOMAS W.

Cholecystic Disease. A Comparison of the Clinical With the Cholecystographic Data Concerning 500 Patients Not Operated On. J. A. M. A., 105:1416, Nov. 2, 1935.

Cholecystography checked by subsequent surgery and pathologic examination has been proven to be a reliable test. There has been some doubt expressed regarding the reliability of cholecystography in non-operated cases.

A series of five hundred such patients examined clinically and cholecystographically but not operated on is here reviewed. The results of this study showed agreement between the clinical impression and cholecystographic findings in 90.8 per cent of these cases.

The results of this study would tend to prove that even in non-operated cases cholecystography is both useful and reliable. Cholecystography should be employed as an aid to the clinical examination. The two examinations can be employed profitably together.

Francis D. Murphy, Milwaukee.

THERAPEUTICS

CLERF, L. H.

Foreign Bodies in the Stomach Removed by Peroral Endoscopy. S. G. and O., Vol. 61, No. 2, pp. 210-213, Aug., 1935.

The Author reports a series of 849 cases of radio-opaque foreign bodies in the stomach and intestinal tract admitted to the Bronchoscopic Clinic of the Jefferson Hospital during a 10 year period ending in January, 1934. Of those, 818 passed spontaneously, 12 were removed by laparotomy, one by peranal endoscopy, and 18 were removed from the stomach by peroral gastroscopy. Among the objects which passed spontaneously were open safety pins, common pins, and a variety of sharp, pointed, and irregular foreign bodies. The Author, aided by a roentgenologist familiar with the technical phase of double plane roentgenoscopy, removed twelve foreign bodies by peroral gastroscopy. He recommends that method when removal is decided upon. In questionable cases the opinion of a competent roentgenologist should be secured to determine if the object can leave the stomach, and also if it will be able to traverse the angulations of the intestinal canal, particularly the duodenojejunal junction..

Nelson M. Percy, Chicago.

WEIR, JAMES F., AND SNELL, ALBERT M.

Symptoms That Persist After Cholecystectomy, Their Nature and Probable Significance. J. A. M. A., 105:1093, Oct. 5, 1935.

Cholecystectomy well performed on proper indications is an extraordinarily successful procedure. The patients who are not cured by cholecystectomy present a very difficult problem. Errors in diagnosis, poor selection of cases, residues of cholecystic disease, cholangeitis, hepatitis, and pancreatitis, stricture formation in the extrahepatic bile passages and post operative colic constitute the basis for poor results.

Careful diagnosis of the presence of gall bladder disease is important. Careful history, physical examination and cholecystography is stressed in making an exact diagnosis. Residual cholangeitis, pancreatitis and hepatitis, in some cases at least, account for poor results after cholecystectomy.

Stricture of the common bile duct after cholecystectomy is a rare cause of complaint.

Colic after cholecystectomy may be explained by stone in the common duct, stricture formation, residual pancreatitis, cholangeitis or hepatitis and in a few cases a spasm of the sphincter of Oddi with transient "physiologic" obstruction.

Francis D. Murphy, Milwaukee.

Dr. Raymond Leaves Rockefeller Institute To Head Searle Research



DR. ALBERT L. RAYMOND

ANNOUNCEMENT

Announcement has just been made by G. D. Searle & Co., Chicago, of the appointment of Dr. Albert L. Raymond as Director of their Research Laboratories.

To take this Searle appointment, Dr. Raymond resigns from the Rockefeller Institute of Medical Research, with which he has been connected for the past nine years, the last seven of which he was an associate of Dr. Levene.

For two years he was National Research fellow, working on problems connected with the biological mechanism of carbohydrate degradation.

Dr. Raymond is a Californian and gained his Ph.D. at the California Institute of Technology, Pasadena, in 1925. Afterwards he spent three years part-time teaching at California Institute of Technology and at the University of California.

He is a member of the American Chemical Society and the American Society of Biological Chemists.

Says Dr. Raymond:
"I know of no field offering greater facilities for the practical application of biochemical research than the laboratory of a pharmaceutical house Here we come in first hand contact with the problems of that working scientist, the practicing physician, and this is a great incentive to provide him with better chemical instruments with which to fight disease." (Adv.)

HOLMES, WM. H.

Medical Treatment of Amoebic Infections of the Liver. S. G. and O., 61:521-522, Oct., 1935.

The hepatic complications of intestinal amoebiasis include acute hepatitis and abscess. The treatment of the former is entirely medical and of the latter, abscess, is almost always surgical. The Author offers good reasons why this should also, in most instances, be treated medically. An amoebic abscess is quite different from a pyogenic abscess in that it results from the lytic action of ferments liberated by amoebae, that it is composed of liquefied liver tissue and red blood cells in various stages of disintegration, and that it does not contain cells of leucocytic origin in uncomplicated cases. The inadequacy of drainage is due in part to the fact that the amoebae are present in greatest numbers in the wall of the cavity and continue enlarging the size of the abscess. Aspiration if not unsuccessful may frequently cause dissemination, and open operation has a rather high mortality rate. Further, contrary to the usual view these abscesses are often multiple increasing the difficulties of either type of surgical drainage. Two patients treated by the Author as well as some reported by others were cured by medical treatment alone. He believes that surgical treatment should be reserved for cases complicated by secondary bacterial infections and for other complications, such as rupture of the abscess into the pleural or peritoneal cavities.

J. Duffy Hancock, Louisville.

ABDOMINAL SURGERY

J. SENEQUE AND MILHIET.

Surgical Treatment of Redundant Colon, in Particular the Precedure in one Stage, with Exteriorized End-to-end Closure. (Traitement Chirurgical du Dolichocolon, en Particulier Dans le Procedure en un Temps, Avec Suture Termino-Terminale Exteriorisee). Jour. de Chir., No. 2, pp. 188-201, Aug., 1935.

In this article the Authors give a general review of the subject of redundant colon, the different operative procedures already made use of, and describe their own technique which they have employed since 1931 in the treatment of five patients with five cures.

Constipation, painful crises, aërocolon, and volvulus, are the indication for operation. However, operative precedure need scarcely be employed in the treatment of constipation as an isolated symptom. The attacks of abdominal pain and aërocolon have the same causes which are especially of mechanical origin, thus by this fact rendering useful surgical intervention. These causes are (1) chronic volvulus and (2) kinking of the intestine; when the patient presents only attacks of pain without meteorism medical therapeutics suffices, in general, to either alleviate or to cure the condition for the lesions of a colitis suffice to explain the symptoms; but when the painful crises are accompanied by colicky distension, the treatment is more delicate.

If the symptoms persist for a long time it may be an indication for resection of the long (redundant) loop in order to remedy the possible twisting or kinking of the loop.

In the cases of intestinal obstruction the resection will be practised either during or after the attack, acording to the case.

For acute volvulus it is possible, by means of the present technique of the Authors, to resect the twisted loop if it is not sphacelated. When the operative procedure is limited to an untwisting of the loop it will be indicated, after the attack, to resect it in order to prevent a recurrence.

The Authors mention the operative procedures already utilized: resection of the rectal valves; dilatation of the anus; section of the first and second lumbar ramicommunicantes; ablation of

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Write for Reprint J. A. M. A., March 4, 1933. Adv.

the right and left lumbar sympathetic ganglia; colopexy; the methods making use of ileo-sigmoidectomy and ileo-rectostomy, with or without exclusion of the redundant loop of colon; sigmoido-sigmoidostomy; all methods inferior to segmental colectomy, the method of choice presenting the minimum of risks.

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Section of the intestine by scalpel close to (or nearly level with) the Kocher forceps.

4th. End-to-end anastomosis, "margin-to-margin" or "border-to-border" of Robineau, the sutures being carried from left to right, and using catgut 00 or linen thread, and a needle at each end.

The Authors describe in details the posterior and anterior musculo-serous and muco-mucous whipstitches.

5th. Careful closure of the mesocolic breach.

6th. Exteriorization of the anastomosis. Two catgut stitches are passed to unite the parietal peritoneum of the angles of the wound with the intestine at a distance of about 4 cms. from the anastomosis at either end, to the level of the colic longitudinal band, if possible. Two large gauze packs are slipped between the two lips of the incision and the intestine. If possible, re-enforce the anastomosis by applying to it a layer of omentum.

7th. Dressing applied on the intestine, vaseline compresses or oily tulle, in order that the intestine and the sutures do not adhere to it.

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terior semi-circumsference. Fistula closed in a second stage. Treatment required 45 days.

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As one is able to gather from the detailed observations of the Authors, the technique recommended by them has the advantages of the two classic procedures without their inconveniences. The technique is simple, the operative results rapid and sure, and the possible rupture of the anastomosis does not expose the patient to any vital danger.

Pierre Smith, Thomas Farmer, Montreal.

STANTON, E. MACD.

Acute Appendicitis. A Study of the Correlation Between the Time of Operation, the Pathology and the Mortality. S. G. and O., Vol. LIX, No. 5, pp. 738-744, Nov., 1934

After having reviewed some recent publications on appendicitis, and after having analyzed and re-analyzed his own, as well as the reported cases of appendicitis during the last twenty-six years, the Author has shaped two functional truths which he believes can be confirmed by any surgeon of experience. The first is that the operative mortality of acute appendicitis bears a definite relationship to the duration of the inflammatory process prior to operation. The mortality increases with the duration of the process up to the fourth and fifth days, which are about the same, after which it falls in a curve almost the mirror image of its rise. The ideal solution of that problem would be to have all patients come to operation during the first twenty-four hours of the attack, but as long as human nature and human judgment remain what they are surgeons will continue to be called upon to treat a considerable number of late cases of appendicitis.

The second basic point is that the mortality is inseparably associated with a corresponding sequence of changes in the inflammatory process itself. During the first day the peritoneal reaction is one of engorgement with little exudate. During the second day there is engorgement and leukocytic infiltration with roughening of the peritoneum. Experience has shown that at this stage the peritoneum is still able to take care of whatever infection there may be after the appendix is removed. During the third day the exudate is distinctly purulent, fibrin is abundant and organization has begun. By the fourth and fifth days the process of organization is well advanced so that the process is somewhat encapsulated. At this stage it is usually multilocular and not drainable; later a single cavity results. As the age of the process increases now, the extent of the peritoneal process diminishes and the mortality rate falls.

In the Author's experience the Ochsner treatment during the high mortality period of the disease has been safe, and technically easy and satisfactory in every way, but it has been morally very difficult not to operate upon most patients as soon as referred. In retrospection the Author believes that he cannot see how he might have materially reduced his mortality rate by employing the Ochsner treatment in a larger number of cases.

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6	Dried Milk	Intolerance Allergy Travelling
7	Acid Milk	Marasmus Diarrhea Celiac Disease
8	Protein Milk	Diarrhea Celiac Disease
9	Butter-Flour Mixture	Marasmus
10	Goat's Milk	Allergy



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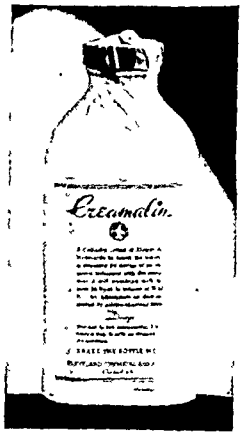
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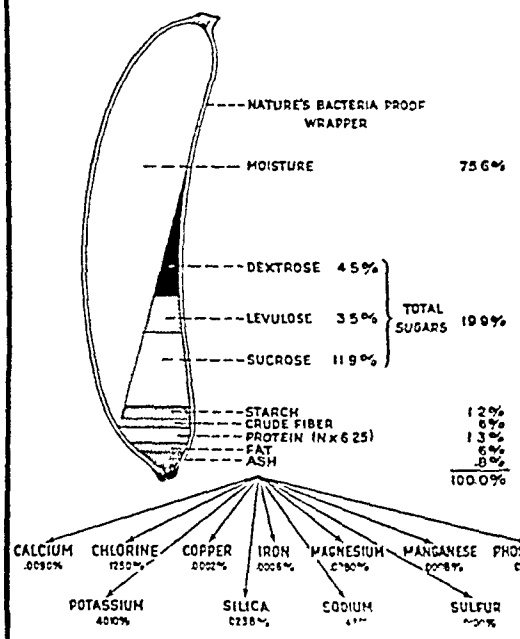
Besides being an excellent source of food energy, bananas are a good source of Vitamins A, B, C, and G, contribute to the diet important minerals and yield alkaline mineral residues in the body. With their soft fiber, pectins, high content of sugars, low content of protein and fat, and their vitamins, bananas seem adapted to act as a normalizer of colonic functioning.

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J D D N 3 3F

"... we know that in the infant and growing child alkali in excess of acid must be stored."

Growth and Development of the Child, Part III, White House Conference on Child Health and Protection, New York, 1932, p. 213.

BUT— many diets are acid-forming

AS pointed out in the Journal of the American Medical Association (Queries and Minor Notes, 103:701, 1934), "... most high carbohydrate foods of the artificial and refined types are lacking in the basic elements. These basic ions, such as sodium, potassium, and calcium, are necessary for the neutralization and excretion of the various acid waste products of the body. Hence carbohydrates may be implicated in the occurrence of such an acid state by displacing other necessary food products from the dietary."

Ordinary cereals and cereal products, meat, and eggs—all produce an acid ash when burned in the body, yet they form the mainstay of the average diet. Although this preponderance of acid-forming foods is not definitely known to have great significance for the health of normal adults, a number of authorities advocate a basic or alkali-forming diet for children and pregnant women.

INFANCY AND CHILDHOOD. "Alkaline diets are essential for infancy where growth is rapid," declares Shohl. *He calculates the need as 10 cc. excess of 0.1 normal base per kilo per day.*[1] *Babies fed on* breast milk stored an excess of base over acid, the range being from 31 to 56 cc. 0.1 N base per day, is the finding of the Committee on Growth and Development of the White House Conference on Child Health.[2] Lippard and Marples observed greater increases in weight of infants receiving basic diets as compared with controls on acid-forming feedings.[3]

PREGNANCY AND LACTATION. Shohl states, "Pregnancy and lactation require additional alkali—a minimum of 150 cc. 0.1 N base per day."[1] Coons and associates, from acid-base balances taken upon normal pregnant women receiving basic diets, determined that the storage of basic substances was even greater than estimated by Shohl. "This may be some indication," they say, "of the magnitude of the maternal needs exclusive of fetus."[4]

As the chief alkali-forming foods are fruits, vegetables, and milk, the ordinary basic diet consisting of these foods is likely to be low in calories and often does not appease hunger. But Pablum—the only base-forming cereal*—offers a way to add muffins, cereal, puddings and similar "filling" foods to the usual basic diet. Pablum, moreover, is richer than ordinary cereals in calcium, phosphorus, iron, and copper and supplies vitamins A, B, E, and G.

[1-4] *Bibliography on request.* *Mead's Cereal (Pablum in uncooked form) is also base-forming.

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PABLUM	1.8	
Farina		11.0
Oatmeal		12.9
Wheat, whole		11.5
Cornmeal		5.3
Barley		10.1
Rice		8.1

Figures given in the above table are based on 100 grams of food and represent cubic centimeters of normal acid or base.

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SECTION I—*Clinical Medicine: Diseases of Digestion*

The Relation in Man Between Gastric Acidity and Height and Weight*

By

FRANCES R. VANZANT, M.D.**
WALTER C. ALVAREZ, M.D.†
and
JOSEPH BERKSON, M.D.‡
ROCHESTER, MINNESOTA

THIS paper represents one of a series of studies of gastric acidity in normal men and women (1, 2, 3, 4, 5 and 6). We are dealing here with the relations of height and weight to free gastric acidity in persons without demonstrable disease of the stomach or duodenum. In making this study we were moved with the desire not only to answer questions that might well be asked by the physiologist or the physical anthropologist, but also to find out if, when comparing mean acidity in two groups of persons, it is advisable to take account of height or weight, or of the degree of thinness or fatness. So far we have not been able to find an adequate answer to these questions in the literature.

For the purpose of this study we picked out from the large mass of data previously used in establishing standards of normal, all those records made on patients who had free acid and for whom note had been made of the height and weight. This selection left us with 2,185 records, 1,228 from men and 957 from women.

GASTRIC ACIDITY AND WEIGHT

In order to see if acidity varies with weight, each person's free acidity was expressed as the difference, plus or minus, between his reading and the normal average for his or her age and sex. These data for men and women separately were then divided into groups representing intervals of 10 pounds (4.5 kg.) in the weight of the persons studied, and in each of these groups the mean deviation in acidity was calculated and plotted as in Figure 1 *B*. Obviously, if there had been no relation between acidity and weight these averages would have all been approximately zero and would have fallen in a straight line running horizontally across the page. Actually, it will be seen that in both men and women there was a small increase in mean acidity with increasing weight, an increase which was more marked in women than in men. In women it amounted to about 0.08 units per pound and in men to approximately 0.06 units per pound. The coefficient of correlation between weight and acidity in this series of observations was, for the women, $+0.346 \pm 0.019$, and for the men, $+0.066 \pm 0.015$.

GASTRIC ACIDITY AND HEIGHT

In looking for a relation between gastric acidity and height the procedure was much the same as that just described; the only difference was that the data representing deviations from normal acidity were divided into groups according to intervals of 2 inches (5 cm.) in the height of the persons studied. Figure 1 *A* shows that in the men there was a rise of 0.8 unit of acidity for each inch of height. No such variation could be found in the case of the women. The coefficient of correlation for the men was $+0.090 \pm 0.019$ which, although very small, is statistically significant. In women the figure was -0.009 ± 0.022 which is not statistically significant.

THE RELATION OF GASTRIC ACIDITY TO NORMAL WEIGHT AND HEIGHT

Unfortunately the data just presented leave several questions unanswered. As we have shown elsewhere, (2, 5) gastric acidity varies with age, and since height and weight also vary with age the question arises: How much of the change in acidity with weight and height is due to the changes in age? If one could study a group of persons all of approximately the same age and height, would gastric acidity still vary with weight, and if so, to what extent? The same questions arise as to the relations between acidity and height in a group of persons of approximately the same age and weight. In other words, we wanted to compare acidity, not with weight alone, but with the degree of fatness or thinness, and similarly, we wanted to study the influence of tallness and shortness.

If we had had thousands of records at our disposal we might have obtained answers to our questions by an analysis of data from groups of persons of the same height (and weight) and age, but even with 2,185 records the method was impracticable because, with three variables to study in men and women separately, the resultant groups would have been too small for reliable statistical analysis. Ordinarily, when faced by such a situation, the statistician uses all his data and

*This work was aided by a grant from the Josiah Macy, Jr., Foundation.
**Division of Biometry and Medical Statistics. Now residing in Houston, Texas.
†Division of Medicine.
‡Division of Biometry and Medical Statistics, The Mayo Clinic.
Submitted November 15, 1935.

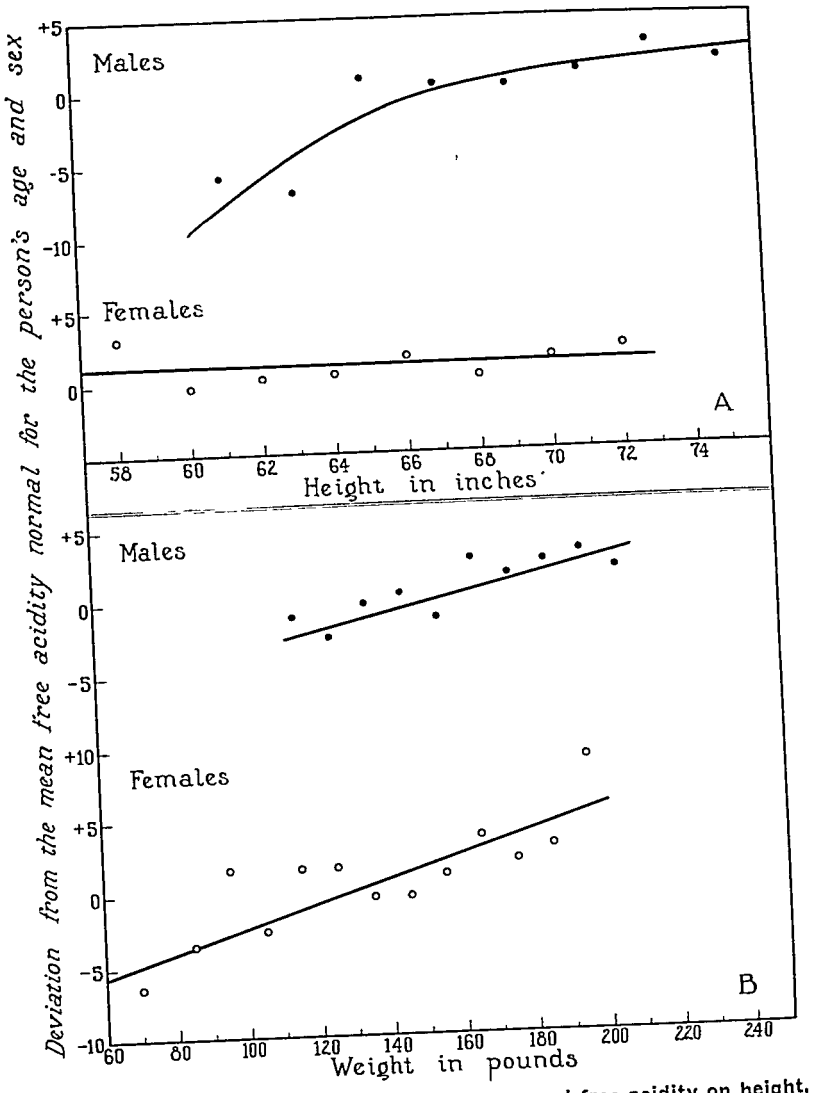


Fig. 1 A. Regressions of deviations from normal free acidity on height, in men and women; B, Regressions of deviations from mean gastric acidity on weight, in men and women.

employs the method of partial correlation, but this can be applied only when the relation of all the variables is strictly linear, and this was found not to be the case with our data, when they were submitted to Blakeman's test.

We first attempted to obtain an answer to the problem by comparing in each case the deviation from the normal standard of acidity with the deviation in weight from the figure given in an insurance table for a man or woman of the given height and age, but a critical analysis of this method showed that it is open to objections. If the insurance standards of height and weight should happen not to apply to the persons included in our study, results might be obtained that would lead to false interpretations respecting the relation of gastric acid to height and weight. Furthermore, one must adhere strictly to certain details in the calculations if the results are to be comparable with those obtained with the use of the partial correlation technic. Accordingly, a method was evolved which is somewhat more elaborate, but gives, we believe, practically the same results for our data as would be obtained by partial correlation if the regressions were linear.

In simple words, we began by preparing a nomogram to give the relationships between age, weight, and height for each sex in our own group of 2,185 persons under investigation. In making this, the data for each sex were separated into groups representing intervals of five years in age, and within each of these groups average weight was plotted against height, and average height against weight. Regression lines were fitted graphically and the height of each man or woman was then expressed as a plus or minus deviation in inches from the mean height for his or her weight and age as determined by the point through which the regression line passed. In the same way individual weights were expressed as deviations in pounds from the mean weight for the given age and height.

These records were then collected in groups representing intervals of 1 inch of deviation from average height and also in groups representing intervals of 10 pounds of deviation from average weight. In each of these groups we next obtained and plotted, as in Figure 2 *A* and *B*, the mean deviation from normal

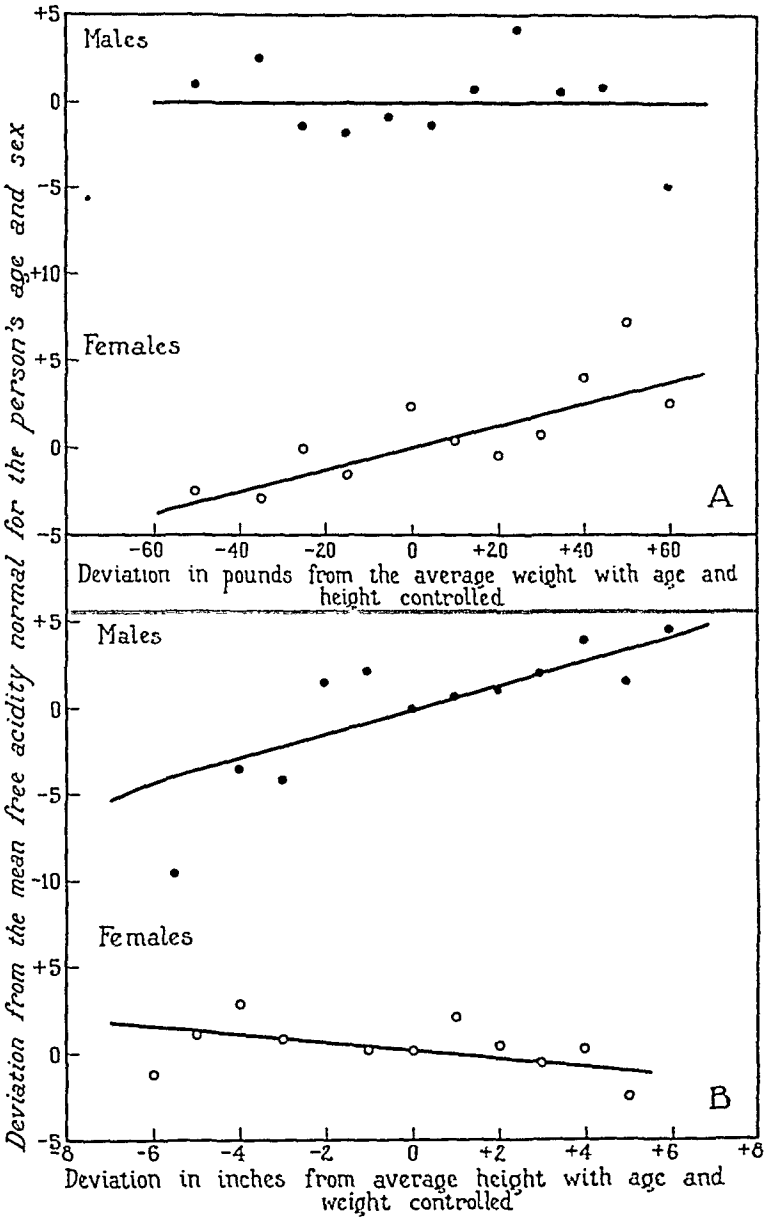


Fig. 2 A. Regressions of deviations from normal free acidity on deviations from average weight with age and height controlled; B, Regressions of deviations from normal free acidity on deviations from average height with age and weight controlled.

free acidity. As the reader will recall, these deviations were obtained by expressing each person's acidity as a difference from his or her normal standard.

It will be seen from Figure 2 *A* that with age and height controlled, there was in women a definite increase in mean gastric acidity with increasing weight amounting to approximately 0.06 units for each pound. Strange to say there was no such relation in the case of men.

Figure 2 *B* shows that in men, with age and weight controlled, gastric acidity increased approximately 0.08 units for every added inch of height. In women there was a slight trend in the opposite direction, amounting to a lessening of acidity of 0.02 units for each added inch in height.

COMMENT

In some work on dogs Vanzant found that when they were fed a standard meal of meat and water the smaller animals tended to have lower curves of acidity than did the larger ones. When, however, the size of the test meal was made proportional to the weight of the dog the response of all the animals was practically the same. It was thought that the larger dogs, with their larger stomachs, would have a larger secreting surface, and perhaps therefore a larger amount of acid to be diluted by the fluid in the standard meal.

Actually this explanation is not adequate to account for the differences seen in the case of man where, during the period between birth and maturity, the body weight increases from twelve to twenty times, the surface area of the gastric mucosa about seventeen times (7), the number of gland mouths about twenty-five times, the number of gland bodies about twelve times (8), and the mean gastric acidity only four or five times. Similarly, with women, the difference between the mean free gastric acidity of those weighing

100 pounds and those weighing 200 pounds is only about 8 units.

The correction factors for differences in bodily build are so small that they need hardly be taken into account unless, when comparing mean acidity in two groups of persons, their mean weights are very different or their mean acidities are very nearly the same. Thus if one group of women were to weigh on the average 20 pounds more than another group, the difference in mean free acidity due to this factor alone would be only 1.2 units.

SUMMARY

A study of 2,185 normal persons showed that, with age and height constant, free gastric acidity increased in women 0.06 units for each added pound of weight. There was no such relation in the case of men. With age and weight constant, free gastric acidity increased in men 0.08 units for each added inch in height. In women the acidity was lowered by 0.02 units for each added inch.

The differences in gastric acidity observed in men and women of widely divergent build are so small that in ordinary practice an allowance need not be made for them.

A simple method of studying multiple correlations when the regressions are non-linear is described.

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New Clinical Concepts of Bacillary Dysentery: Its Relationship to Non-specific Ulcerative Colitis, Distal Ileitis and Non-specific Granuloma.*

By

JOSEPH FELSEN, M.D.

NEW YORK, NEW YORK

THE following data (1) are from studies made in the eighteen month period from December, 1933 to June, 1935, of 317 cases of acute bacillary dysentery, 11 cases of acute distal ileitis, 42 consecutive cases of non-specific ulcerative colitis, 8 with chronic distal ileitis, 4 with pseudo-polyposis (polyposis cystica of Virchow) and 2 cases of non-specific granuloma of the ileocecal region. A follow-up is included in this study and the evidence is presented in an attempt to show that acute bacillary dysentery, acute distal ileitis, chronic non-specific ulcerative colitis and ileitis and non-specific granuloma are but different stages of the same disease.

Typical Acute Bacillary Dysentery. The typical case of acute bacillary dysentery presents intestinal manifestations and systemic toxic effects which are prominent, easily recognized and require only bacteriologic study for accurate corroboration. The patient is placed on typhoid precautions, an epidemiologic survey is made and in the average mild or moderately severe case the disease runs its course in approximately seven to ten days with complete recovery. Only certain features, frequently overlooked, will be stressed. First, the incubation period is often a matter of hours rather than days. In two specific instances where the actual contact was proven, one of Flexner and another of Sonne-Duval, the incubation period was approximately 14 and 10 hours respectively. Second, the highly toxic Shiga type of dysentery is relatively infrequent in the United States but the Flexner group may sometimes be found to equal the former in toxicity, to say nothing of the occasional instances of sudden death in the comparatively mild Sonne-Duval type. Third, acute multiple arthritis is a rather common complication of bacillary dysentery and often persists in the chronic stage (12% in our series. See Table I). Fourth, the diagnostic laboratory criteria are positive fecal culture during the first week and bacteriophage and rising agglutination titre after the first week. Also, an initial leucopenia is relatively common in acute bacillary dysentery. We have seen counts as low as 3600 in moderately severe cases with complete recovery. Fifth, local as well as national statistics on bacillary dysentery are incomplete because intramural institutional outbreaks are neither properly studied nor are the clinical manifestations easily recognized by the physician who sees the atypical epidemic or sporadic cases. We shall refer briefly to these atypical types.

Atypical Acute Bacillary Dysentery. 1. Neurotropic type. Symptomatology resembles that of meningococcus meningitis but the spinal fluid findings are negative. The patient has or soon develops an intractable diarrhea. Nasal or labial herpes is present. 2. Appendicular type. Symptomatology resembles that of

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acute suppurative appendicitis but at operation the appendix is found to be normal. There is seen, however, an acute diffuse mesenteric lymphadenitis and usually an acute segmental inflammation of the distal ileum. A normal leucocyte count or leucopenia, pain and tenderness in the ileocecal region without abdominal rigidity, and the presence of spastic ileum or sigmoid are the chief differential features. The occasional association of an upper respiratory infection with mesenteric lymphadenitis in acute bacillary dysentery in children is noteworthy. 3. Afebrile type. 4. Asymptomatic type. These patients are not carriers. 5. Constipated type. To these types, the recognition of which is so important in the epidemiology of the disease and its relationship to chronic intestinal

TABLE I

Agglutination Titre in 42 Consecutive Cases of Non-Specific Ulcerative Colitis

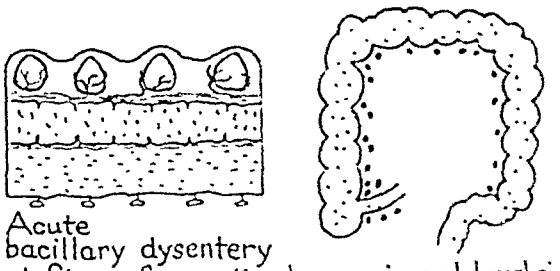
Patient	Duration (years)	Titre	Remarks
1	7	P-H 1:320	
2	2½	Mt. D 1:160	
3	1	S-D 1:160	
4	10	Mt. D 1:160	
5	1	Mt. D 1:80	
6	1½	P-H 1:160	Ileitis. Resection.
7	1	Mt. D 1:80	2 contacts.
8	11	S-D 1:10	
9	2	F 1:160	1 contact.
10	14	F 1:800	Ileitis. Resection.
11	1	P-H 1:320	Phage. Arthritis.
12	6	Mt. D 1:160	Phage
13	2½	Mt. D 1:320	
14	5½	P-H 1:640	Non-specific granuloma. Resection.
15	2	P-H 1:80	
16	4	Mt. D 1:160	Arthritis Neuritis.
17	5	Mt. D 1:80	1 contact
18	½	S-D 1:100	Ileitis.
19	1	F 1:320	J. C. ep.
20	6	F 1:320	3 contacts.
21	4	F 1:100	Phage.
22	10	Mt. D 1:320	8 contacts: 1—Mt. D 1:320 2—Mt. D 1:160 F 1:320
23	1	Mt. D 1:160	
24	1	Mt. D 1:160	
25	2	F 1:160	Ileitis
26	2	Mt. D 1:80	
27	5	S-D 1:40	Phage.
28	1½	F 1:160	1 contact. Phage Arthritis.
29	1	Mt. D 1:160	Polyposis.
30		Mt. D 1:640	Ileitis Non-specific granuloma. Resection.
31	7	F 1:160	Polyposis
32	5	P-H 1:240	Phage
33	3	Mt. D 1:160	Phage.
34	2	P-H 1:320	Ileitis. Polyposis
35	½	Mt. D 1:320	
36	1	F 1:160	Ileitis.
37	½	F 1:160	
38	10	P-H 1:160	Ileitis. Resection. B. dys. in feces Phage Mt. D.
39	1	Mt. D 1:120	Arthritis.
40	?	Mt. D 1:320	Phage S-D
41	1½	Mt. D 1:640	Arthritis
42	7	Mt. D 1:160	Ileitis.

SUMMARY

A. *Non-Specific Ulcerative Colitis and Ileitis (42 consecutive cases).*

	Cases	%		
Mt. D and P-H	27	64	Arthritis	5 (12%)
S-D	5	12	Ileitis	9 (21%)
Flexner	10	24	Non-specific granuloma	2 (5%)
	42	100		

B. *Controls* 300 (New York City area).
Diagnostic titres 4.6% (all types). None against S-D.

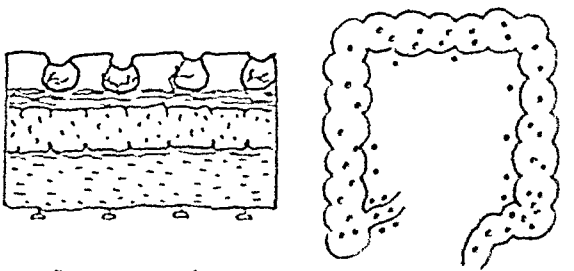


Acute bacillary dysentery

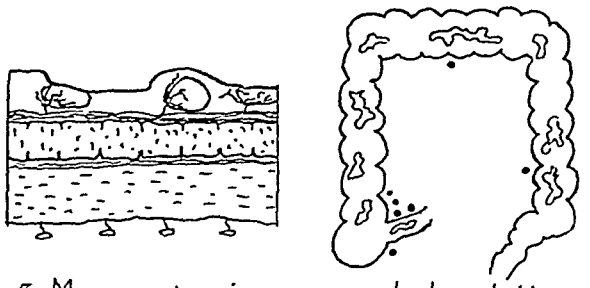
1. Stage of congestion, hyperemia and lymphoid hyperplasia; acute distal ileitis, mesenteric and mesocolic lymphadenitis.

ulceration, there may now be added another type, viz., 6. Acute fulminating type with malignant neutropenia. The two cases thus far encountered were of the Flexner and Mt. Desert types, the disease running its acute course to a fatal termination in three to four weeks. Advanced ulcerative ileocolitis with pseudo-polyposis was present in both cases, the toxemia was profound and was associated with a progressive decrease in leucocytes and neutrophiles and marked toxic changes in the latter. There was extreme dehydration with a misleading hemoglobin-erythrocytic picture due to blood concentration. In one case a Vincent's infection of the mouth was definitely present, in the other no examinations for the organisms were made although mouth lesions were present. The association of the neutropenia with the Vincent's infection is possible but our frequent observation of marked leucopenia in other cases of acute bacillary dysentery without a secondary Vincent's infection militates against this relationship. It appears rather to be due to destruction of the granulocytes by the dysentery toxin in the peripheral blood or to a toxin effect on the vascular sinusoids of the bone marrow into which the granulocytes must pass after their extravascular formation. This is further supported by the finding that bone marrow sections showed no lack of production of granulocytes. We have noted similar effects upon the blood vessels and reticulo-endothelial tissue of the intestine in humans and animals.

Relationship of Acute Bacillary Dysentery to Chronic Ulcerative (Non-specific) Colitis, Distal Ileitis and Non-specific Granuloma. Bearing in mind the facts briefly alluded to above regarding the typical and atypical phases of acute bacillary dysentery it may be readily understood why much confusion has arisen with regard to the other diseases named. It is due chiefly to: 1. Non-recognition of the disease in the acute stage. 2. Lack of adequate follow-up of the diagnosed cases. It is the latter upon which we must



2. Focal lymphoid necrosis with punctate ulceration and superficial mucosal denudation



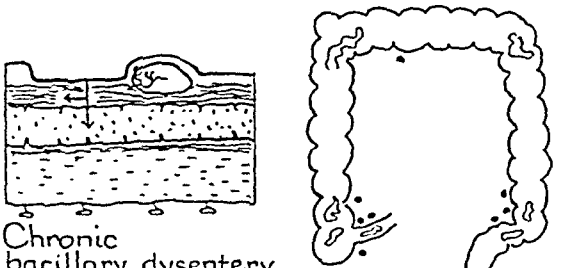
3. More extensive mucosal denudation. Confluent ulceration.

rely chiefly and, supplemented by a thorough knowledge of the underlying pathology, accurately link the acute and chronic stages hitherto regarded as specific and independent diseases. To this end we have followed up our acute dysentery cases and with the information thus gained have studied or re-studied our cases of chronic non-specific ulceration. Each case was investigated as follows: General physical examination with special reference to abdominal masses and intestinal spasm, fecal or sigmoidoscopic culture, diagnostic bacteriophage, agglutination titre, examination for endamoeba histolytica cysts and trophozoites, sigmoidoscopic examination, roentgenographic study of the intestinal tract and epidemiologic investigation. The follow-up was along the same general lines. Young children were not sigmoidoscoped as a rule and roentgenographic examinations were made only in those acute cases where some indication existed. This data may be briefly summarized as follows:

1. Most of our cases of acute bacillary dysentery recovered completely in ten days to two weeks.

2. Acute distal ileitis appeared to subside but in some cases the intestinal lesion persisted. In one child a mass was still palpable at the end of four months, associated with recurrent attacks of bloody diarrhea.

3. Cases of acute baciliary dysentery lasting for more than three weeks appeared to persist by reason of a secondary non-specific infection. Seven patients followed from the time of their initial dysenteric infection had the typical signs and symptoms of non-specific ulcerative colitis at the end of approximately 1, 1, 1, 1, ¾, 1 and 1 year respectively. One patient (Case 14, Table I) had an acute inflammation of the distal ileum and cecum with mesenteric lymphadenitis for which a laparotomy was done in January, 1930. A typical chronic non-specific granuloma was removed three years later at the Bronx Hospital. The interval period was characterized by periodic attacks of bloody and mucoid diarrhea and abdominal cramps.

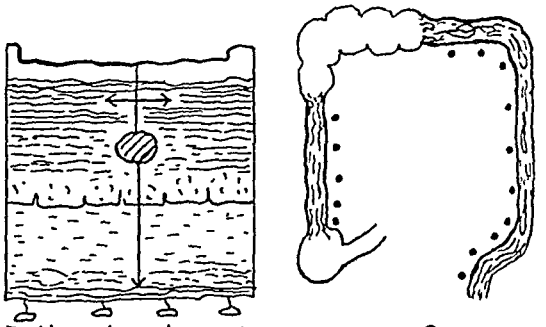


Chronic bacillary dysentery

4. Acute lesions have not entirely subsided. Secondary non-specific intramural infection begins (probably after third week)

4. In six cases of non-specific ulcerative colitis seen for the first time at varying periods after their initial acute infection definite contact infection was demonstrated suggesting that non-specific ulcerative colitis is transmitted only during the initial stage—namely, that of acute bacillary dysentery.

5. In forty-two consecutive cases of non-specific ulcerative colitis a diagnostic agglutination titre against B. dysenteriae was obtained. In control studies (2) of 300 persons in the New York City area without a history or clinical evidence of dysentery only 4.6% of diagnostic titres was demonstrated. The colitis and control groups were studied by the same method and identical dysentery strains. Eighteen hour broth



Fully developed non-specific ulcerative colitis

5. (a) Inflammatory polyposis with massive geographic and serpiginous mucosal denudation
(b) Mural fibrosis with loss of haustration. Often segmental.
(c) Stenosis of lumen of bowel.
(d) Extensive mural infection, intramural abscess, perforation.

cultures of smooth agglutinable strains, four hours incubation at 55 C. and overnight ice box incubation were used. In certain cases, as specified in Table I, diagnostic phage or positive fecal culture was demonstrated. In one case, a physician with a history of ten years standing, a resection had been done for chronic distal ileitis. Examination of the gross specimen and microscopic sections showed the typical lesion, and phage and culture was positive for B. dysenteriae, Flexner. He had been having recurring attacks of diarrhea with only temporary remissions both pre- and post-operative for ten years.

6. Of the cases included in this report a pathologic study was made of seven specimens of acute bacillary dysentery, eleven of acute distal ileitis*, six of chronic distal ileitis, two of non-specific granuloma and seven of non-specific ulcerative colitis. The lesions in the chronic stage were identical with those seen in acute bacillary dysentery except that owing to the long duration of the disease extensive fibrosis and intramural infection were present. The former represented Nature's attempt at healing and accounted for the loss of haustration and stenosis seen in chronic distal

*Observations at the operating table, sections of mesenteric nodes and appendix supplemented by cultural studies.

ileitis and non-specific ulcerative colitis. Non-specific granuloma of the ileocecal region represents a productive type of inflammation and, like chronic distal ileitis, almost always shows giant cells in the tissue sections. This condition may be erroneously diagnosed as tuberculosis but tubercle bacilli are absent and guinea pig inoculation of the macerated tissue proves negative. The transition stages from the acute enterocolitis of bacillary dysentery to the chronic non-specific lesions are diagramatically shown in Figures 1-7. The acute or chronic lesions may show segmental involvement of the jejunum or ileum, the former being rare.

7. While no case of amoebic dysentery has been included in this study it appears quite probable that the same type of secondary non-specific infection might occur. Those cases with distal ileitis, however, cannot be included as the endamoeba histolytica does not attack the terminal ileum. No case of double infection with both bacillary and amoebic dysentery has come to our attention. Two cases of double infection with typhoid and Sonne-Duval dysentery were seen. Both patients recovered completely.

TABLE II

Agglutination Titre in 11 Cases of Acute Distal Ileitis with Mesenteric Lymphadenitis

Patient	Durntion (days)	Titre	Fecal Culture
1	8	F 1:100	Flexner.
2	21	F 1:100	Flexner.
3	10	F 1:100	
4	3	S-D 1:200	S-D phage.
5	7	S-D 1:160	S-D phage and culture.
6	2	S-D 1:100	
7	1	S-D 1:640	S-D.
8	14	F 1:160	
9	1	F 1:100	
10	1	F 1:100	
11	14	S-D 1:100	

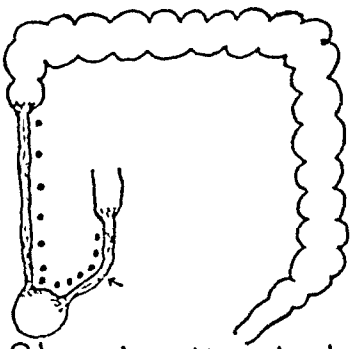
SUMMARY

Flexner: 6; S-D: 5.

Abbreviations: P-H (Park-Hiss strain), Mt. D (Mount Desert strain), S-D (Sonne-Duval strain), F (Flexner strain), J. C. (Jersey City strain) (Flexner). It should be noted that while 1:100 is generally regarded as a diagnostic titre in bacillary dysentery, only 1:40 or 1:50 is required for the S-D strain.

8. Attention is called to the peculiar "stooped-over" or mendicant's posture exhibited by many long standing cases of non-specific ulcerative colitis.

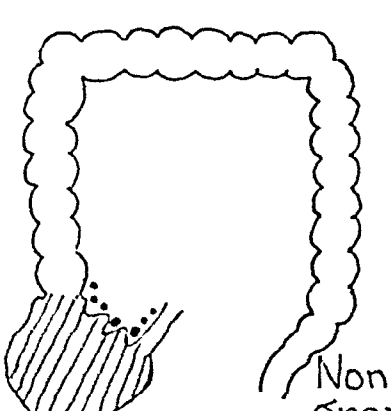
Treatment. The ideal treatment of non-specific ulcerative colitis and its related lesions appears to be the prevention of bacillary dysentery. Recognition of the typical and atypical forms of the disease, prompt isolation and careful epidemiologic surveys should, so far as our studies indicate, lessen the incidence of the diseases known as non-specific ulcerative colitis, chronic distal ileitis and non-specific granuloma. Basically, it is a public health problem. At the Bronx Hospital we suggested paying the nursing and lay staff relieved from duty because of diarrhea so that there should be no hesitancy in reporting for examination. Monthly surveys are being made of all foodhandlers. Institutional outbreaks are frequent because they are not recognized or studied, because the management dislikes the publicity or because employees hesitate to report sick for fear of losing their pay. Every patient with diarrhea or a history of diarrhea should be placed on typhoid precautions until proven free of B. dysenteriae. This is particularly important among children.



Chronic distal ileitis

6. A stenosing, obstructive lesion with fibrosis. Granulomatous giant cells often present. May be mistaken for tuberculosis.

Most cases of acute bacillary dysentery recover without any specific therapy. Supportive treatment, daily doses of castor oil to favor elimination of the toxin and intravenous infusion of 5% dextrose in saline or transfusion for dehydration and toxemia may be used when indicated. The use of recently recovered cases as donors is suggested in the acute severe types of the disease. All patients with acute bacillary dysentery in whom the intestinal lesions persist for more than three weeks should be placed immediately upon prophylactic D-C vaccine and antivirus therapy. In sporadic or epidemic outbreaks the widespread use of polyvalent dysentery vaccine should afford some degree of immunity *before* the patient becomes infected. This observation is based upon a limited experience with human contacts and experimental animals. Some cases of non-specific ulcerative colitis heal spontaneously but most of them go on for years with periodic stages of remission and exacerbation. For the latter we have outlined a course of therapy which has proved quite efficacious. It must be remembered that all we can hope for in a case of long duration where the intestine is really nothing more than a tube of vascularized connective tissue free of protective lymph nodules and with diffuse infection or intramural abscesses, is subsidence of the infection. Towards this end we use the following therapy: 1. Intestinal oxygenation. 2. D-C



Non-specific granuloma

7. Productive type of inflammation Granulomatous giant cells may be present.

vaccine. 3. D-C antivirus. The organisms in the vaccine and antivirus include polyvalent strains of the specific dysentery (D) organism with which the patient was originally infected as demonstrated by the agglutination titre, and the two common secondary invaders, enterococcus and B. coli (C). The vaccine and antivirus are administered every other day, the former in gradually increasing dosage after a preliminary skin test for sensitivity. A D-C serum is now in process of preparation for quick passive immunization. Therapeutic phage has proven of little value and surgery of very limited usefulness. Resections in our experience have almost invariably been followed by recurrences because the surgeon cuts through infected bowel. It is surprising how far intramural infection actually extends beyond the grossly visible line of pathology. Surgery is indicated chiefly in acute obstruction. It is preferable to handle the disease by preventing bacillary dysentery, following up the cases that do occur so as to forestall the late lesions which, when they do become manifest, are best treated by the systemic route through which the original infection took place.

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Studies on Constitution and Peptic Ulcer

I. Appetite Secretion in Normal Persons and in Ulcer Patients*

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and

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FOR almost a century, physiologists have accumulated evidence indicating that gastric secretion is markedly influenced by psychogenous stimuli.

In 1833, Beaumont (1) had already suspected a nervous factor in gastric secretion. Some two decades later, Bidder and Schmidt (2) demonstrated that the perception of food sufficed to stimulate a flow of gastric juice, but it was left to Pavlov (3) to recognize this phenomenon as a true cerebral reflex. In 1887, Pavlov and Schumov-Simanovskaia (3) described the now classic "sham feeding" experiments, which utilized esophagotomized and gastrostomized dogs who were allowed to masticate food which, when swallowed, fell out through the peripheral esophageal fistula, thus permitting the collection of an uncontaminated gastric juice.

Analogous experimentation has been done with man as subject. In 1878 Richet (4) detected a psychic secretion in a young man with an esophageal stenosis and a gastrostomy. Subsequent work, reviewed and extended by Carlson (5), Babkin (6), and others (7-8) has established that "sham feeding" of palatable foods will stimulate gastric secretion in man, but that indifferent or repulsive material will not.

The first determination of the volume and acidity of the psychic secretion in an ulcer subject was made by Troller (9) in 1899, who merely demonstrated that a psychic secretion does exist. Subsequently, a number of clinicians (10-14) have recommended the clinical employment of "sham feeding" to detect states of hyperacidity and hypersecretion as well as hyperirritability of the gastric vagus.

In this connection, the theory of Moszkowicz (15) must be mentioned. Basing his conclusions upon the work of Silbermann (16) who produced ulcers in dogs by persistent "sham feeding" he has conceived the thesis that a continuous high acid psychic secretion is the causative agent in peptic ulcer.

TABLE I

Age Distribution in Appetite Secretion Series

Age in Years	Number of Patients	
	Normal	Ulcer
17-20	4	2
21-30	7	6
31-40	10	10
41-50	6	7
51-60	7	7
61-70	1	2
Total	35	34

To our knowledge, no one has described as yet, the comparative appetite secretion between normal subjects and patients with peptic ulcer. The present study represents such an investigation of the appetite secretion of 34 male subjects with duodenal ulcer, the diagnosis of which was established roentgenologically, and of 35 normal men. The age distribution in both groups is practically identical.

METHOD OF PROCEDURE

All individual determinations were performed under similar conditions, in the same room, and at approximately

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the same morning hour. The subjects were not told the purpose of the investigation.

The preliminary instructions to the subjects were to eat nothing after 10 o'clock the night preceding the test and to drink nothing the morning of the examination.

For the test proper, the patient assumed a comfortable semi-reclining position; a Rehfuss tube was passed into the stomach; and the residual gastric contents evacuated, measured and titrated. At ten minute intervals, in the succeeding half-hour, aspirations were made of the basal stomach secretion, its volume determined, 10 c.c. was retained for titration, and the remainder returned to the stomach.

Following the last control determination, the subject was provided with a chilled orange broken into small pieces, and given instructions to chew the orange slowly, to swallow nothing, and to expectorate the orange pulp, the orange juice, and saliva. The time given for mastication was ten minutes.

Immediately thereafter, the entire gastric contents were aspirated, examined for orange contents, measured, titrated and not returned. Subsequently, at five ten minute intervals and one final 30 minute interval, 80 minutes in all, the stomach was completely emptied, the volume determined, 10 c.c. set aside for analysis and the remainder returned.

The data accumulated in this manner were analyzed statistically (formulae of Fisher 17). The mean free and total acidity and the mean secretion volume for the group of ulcer patients and normal persons respectively were compared before and after the "sham" meal at each of the time intervals specified above. The basal secretion is considered as the average of the last two control specimens before the "sham" meal.

RESULTS

The results obtained can be easily understood from Chart 1, where each point represents the mean of all determinations. It is apparent that the acidity not only rises immediately following mastication of the orange and later returns to a basal level, but also that in a general way the behavior of the ulcer and normal subjects varies only quantitatively. This similar reaction of appetite secretion in both groups is sufficiently consistent to indicate the expression of an intrinsic physiologic mechanism, which is not disturbed by the disease "ulcer," and is shifted to a higher level. This reaction distinctly parallels the response of normal persons and of patients with duodenal ulcer to an Ewald meal, and the curves and explanations given by Vanzant, Alvarez and Eusterman (18) are strikingly similar to these curves of psychic secretion. Even the difference in free acidity, determined by a test meal, between their groups of normal persons and of ulcer patients is quite similar to the difference in the free acidity of appetite secretion observed here.

Table II indicates that no significant difference exists in basal acidity between ulcer and normal subjects, but that the appetite juice collected 10 and 20 minutes after the beginning of mastication is 12.8 and 14.8 degrees respectively higher in free acidity for the ulcer group, and these values are statistically significant. The total acidity reflects this phenomenon, as manifest in the borderline significance of 11.3 degrees difference between ulcer and normal subjects in the first 10 minute specimen.

TABLE II

Appetite Secretion in Normal Persons and in Ulcer Patients

		ACID SECRETION OF STOMACH						
		Before[1]	After Chewing of Orange (in Minutes)					
			10	20	30	40	50	80
FREE ACIDITY	Ulcer Mean	26.1	28.6	35.2	35.7	32.6	33.4	27.4
	Normal Mean	16.9	15.8	20.4	25.7	26.0	23.5	27.6
	Difference of Means	9.2	12.8	14.8	10.0	6.6	9.9	-0.2
	Significance of the Difference of Means	n.s.[2]	±5.09 (s)[3]	±4.8 (s)	n.s.	n.s.	n.s.	n.s.
TOTAL ACIDITY	Ulcer Mean	46.4	61.0	63.9	62.6	57.1	56.3	49.4
	Normal Mean	39.6	49.7	48.5	51.7	50.1	44.1	44.5
	Difference of Means	6.8	11.3	15.4	10.9	7.0	12.2	4.9
	Significance of the Difference of Means	n.s.	±5.9 (s)	n.s.	n.s.	n.s.	n.s.	n.s.

The Acidity is expressed in clinical degrees, i.e. in c.c. of N/10 HCl per 100 c.c. of gastric juice.
[1] Average of two ten minute periods before mastication.
[2] Not significant.
[3] Significant.

The difference in mean volumes never proved statistically significant.

The above results indicate that the ulcer subject reacts excessively to an ordinary stimulus. Further, it appears that human appetite juice is a secretion of only small volume, of short duration (20 minutes) and of moderate acidity, hardly possessing the properties attributed to it by Moszkowicz (15).

The extreme variability in the individual values obtained throughout both ulcer and normal series completely vitiates the significance of "sham feeding" utilized for clinical diagnostic purposes. Undoubtedly

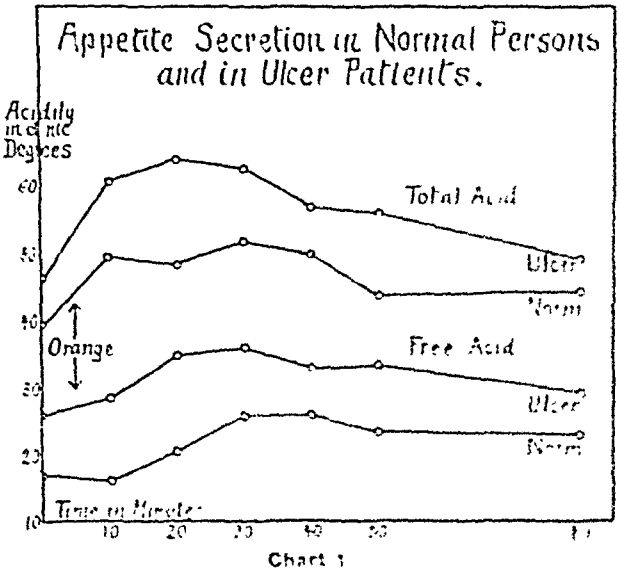


Chart 1

the variability of psychic secretion depends, in considerable measure, upon the methods employed. The foreign environment, the nausea evoked in some subjects by the stomach tube, the relative hunger at the time of the test, the relative preference for the test meal, the frustration experienced in avoiding deglutition and in expectorating the desired food, the difficulty in aspirating very small quantities of gastric juice, the variations in regurgitated duodenal contents and in some unavoidably swallowed saliva—all these factors modify any single determination. Only a sufficient number of individual examinations, interpreted statistically, can disclose the actual physiologic tendency.

The significance of this moderate increase of psychic secretion for the genesis of peptic ulcer is not obvious. The moderate acidity demonstrated here as the mean for the ulcer patient tends to corroborate the view of Majus and Porges (19) that appetite secretion is only secondary in importance to the gastric phase of secretion. The brief duration of the appetite secretion indicates that psychic factors are probably not concerned in the greater acid response to an Ewald meal exhibited by ulcer subjects from 1 hour to 1½ hours after ingestion. Chemical secretagogues appear more significant. Seemingly, appetite secretion is much less in quantity and in duration for man than for dog.

The results presented here may be explained in one of two ways. Either the "ulcer stomach" responds excessively to normal vagal stimuli reaching it during mastication or too many stimuli may be conveyed to it along the vagi during this process. This latter interpretation is consistent with the possible existence of vagotonia in peptic ulcer subjects.

SUMMARY

Appetite secretion was produced by "sham feeding" in a group of 35 normal healthy individuals and in a group of 34 patients with peptic ulcer of the duodenum.

During the first twenty minutes, after the mere chewing of an orange, the mean acidity of the group of ulcer patients was significantly higher than that of the group of normal persons. The higher level of appetite secretion in patients with peptic ulcer is similar to the response of this group to an Ewald meal.

The moderately higher acidity of appetite juice of ulcer patients does not warrant giving it a rôle in the genesis of peptic ulcer. Because of its variability, appetite secretion cannot be an aid in the diagnosis of duodenal ulcer.

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Studies on Constitution and Peptic Ulcer

II. The Dermographic Time of Peptic Ulcer Patients and Normal Subjects*

By

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THE hypothesis that ulcer originates in vascular spasm of the stomach and the duodenum suggested that a general disturbance in vaso-motor tonus of ulcer patients might be detected in the type of skin response to stimulation, as expressed in dermographic reaction time. The term "dermographism," as used in this paper, denotes merely the appearance of a red streak upon the skin in response to stimulation.

An extensive literature on cutaneous vascular phenomena has been critically reviewed by Krogh (1) and Lewis (2), and will not be surveyed here. It would appear that capillariomotor function regulated as it is by an intricate nervous and humoral mechanism should constitute a sensitive indicator of some imbalance in the vasomotor system. Kraft-Ebing (3) has stressed

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the vasomotor lability of the nervous individual and described the skin writing and wheal formation which may occur. Moebius (4) has observed that hyperthyroid subjects blush easily; and Nothhaas (5) has suggested a relation between dermographic reaction time and basal metabolic rate.

MATERIAL AND METHOD

The subjects of this research were 80 patients with duodenal ulcer (64 males and 16 females); the diagnoses having been established by X-ray; and 62 normal individuals as controls (60 males and 2 females). The routine procedure consisted in exposing the intrascapular region for 30 minutes so as to acclimatize the skin to room temperature, then stroking the skin between the medial border of the scapula and the lateral edge of the vertebral transverse processes, and timing the appearance of the red streak. Russetski (6) has indicated that the skin of the chest and back reacts most intensively to given stimulation.

The instrument used in this operation, devised by Nothhaas (5) consists of two parallel bars supporting a vertical rider which moves between them, and which by means of an inner regulatable spring can be made to impinge upon the skin at a measurable and constant pressure (115 grams). Four readings of skin reaction-time were taken on each subject, and in many instances, duplicate readings were taken on subsequent occasions; these checked closely in most instances. The formulae of Fisher (7) were employed in the statistical treatment of the results presented below.

RESULTS

A significant difference between normal and ulcer subjects occurs if comparison is made between the entire ulcer and normal groups, irrespective of varying age distribution in both populations. The dermographic time for ulcer and normal subjects was 12.8 and 10.6 seconds respectively.

If, however, age groups are compared, no significant difference in dermographic reaction-time is evident between normal individuals and ulcer patients of similar age.

This disappearance of a difference in reaction-time, upon subdividing both groups into age categories, demonstrated that age represents an important factor in dermographism. Being identical in reaction-time, both groups, normal and ulcer were united, subdivided into age groups, which were compared statistically with one another. Here it became evident that a marked increase in dermographic reaction-time occurs with advancing age.

The results in Table I indicate clearly that the most rapid skin reaction occurs below thirty years of age (9.8 seconds); that the skin reaction is considerably retarded above this age; and that no significant difference obtains between the middle age group of 31-50 years (13.4 seconds) and the older age group of 51-70 years (15.4 seconds).

In no instance, and this includes the ulcer series, was wheal formation observed. There was no significant difference between sexes and no correlation between blood pressure and dermographic reaction-time. It may be noted here that, with few exceptions, all ulcer patients had low or normal blood pressures.

The identity of skin response in ulcer and normal subjects seems contradictory to the theory of von Bergmann (8) and others (9) that peptic ulcer is the resultant of a neuro-spastic tendency, as well as being inconsistent with the findings of Müller (10) that the arterioles, capillaries and venules in the skin, lips and stomach of ulcer subjects are tortuous, irregular and varicosed. It may be, of course, that the method employed here is inadequate for detection of the spasticity that may actually characterize the blood vessels of the ulcer subject, although it appears improbable that

TABLE I

Dermographic Reaction Time

Group	Age in years	No. of Subjects	Dermogr. Reaction-Time Means and Standard Error (Secs.)
A	12-30	45	9.8 ± 0.47
B	31-50	64	13.375 ± 0.724
C	51-70	33	15.424 ± 0.949

Difference of Means

Age Group	Difference of Means and Standard Error
B-A	3.575 ± 0.874
C-A	5.626 ± 0.972
C-B	1.952 ± 1.01157

a marked tonus of the capillaries would not alter the dermographic response in some manner.

The significance of the delayed capillary dilatation in the older age group still remains for speculation. Fundamentally it indicates a difference in capillary reactivity between older and younger individuals. Apparently the capillaries of an individual about 30 years of age require a longer interval for dilatation to develop in response to stimulation. Conceivably this might result from either a preponderance of the sympathetic-pituitary-adrenal constricting mechanism, or a deficiency of the antidromic-histamine dilating mechanism.

The experimental results of this paper may offer a partial explanation for the greater incidence of peptic ulcer above about 30 years of age, but they do not actually conform with the von Bergmann (8) theory of a general vasomotor disturbance in ulcer patients.

SUMMARY

No difference in dermographic reaction-time was found between a group of 80 ulcer patients and a group of 62 normal subjects.

There is a distinct relation between dermographic reaction-time and age. Until 30 years of age, derma-

graphic reaction-time is relatively short (9.8 seconds). Above this age, it slows down abruptly (13.4 seconds for the age group of 31-50 years) and then remains relatively constant (15.4 seconds for the age group of 51-70 years). This signifies an alteration with age of the capillaries of the skin and therefore, probably, of the skin itself.

The possibility of a correlation between incidence of peptic ulcer and changes in dermographic reaction time with age is discussed.

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SECTION II—*Experimental Physiology*

A Study of the Effect of Anoxemia on the Pyloric Sphincter in Unanesthetized Dogs*

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IN 1933 it was reported that anoxemia caused a delay in the emptying time of the stomach in normal dogs (1). In a subsequent paper (2) it was shown that the effect of anoxemia on the pyloric sphincter of barbitalized dogs was inconstant. Further work was attempted on the mechanism of delay in gastric emptying time caused by anoxemia. This work (3) indicated that the delay at low degrees of anoxemia was at least partially caused by a pylorospasm, probably of a vagospastic nature, while the greater delay encountered at the higher degrees of anoxemia probably involved the added factor of a direct depression of the gastric musculature by the anoxemia.

In view of these findings it was thought well worth while to make a study of the effect of anoxemia on the pyloric sphincter in unanesthetized animals.

METHODS

Two previously operated dogs were used in this experiment. These animals each had two abdominal fistulae, one opening into the proximal part of the duodenum, and the other opening into the stomach. A rubber tube was placed in each of these openings, the two tubes being connected by a collapsible section at the pylorus and attached to a pressure tonometer and recording device as described in 1929 (4). It was thus possible to make simultaneous, synchronized tracings of the tone and the contractions of both the pyloric sphincter and the pyloric antrum.

Anoxemia was produced by allowing the animals to breathe from a rubber bag, connected with an apparatus previously described (5) for mixing oxygen and nitrogen in the desired proportions. A flutter valve was inserted in the otherwise closed system, allowing the animal to expire to the outside, thus preventing the accumulation of carbon dioxide.

During the control periods the animals were allowed to breathe a gas mixture containing 20% of oxygen. Anoxemia was administered by reducing the oxygen to the desired percentage without changing the total pressure within the system. The oxygen percentages used in this experiment were: 6%, 9%, and 14%, respectively.

Attention was, of course, given to all mechanical and other details essential to accurately controlled anoxemia, and to uniform experimental conditions.

RESULTS

For convenience in presentation, the results obtained will be given in sections, according to the degree of anoxemia.

6% OXYGEN

Seven determinations were made upon the pyloric sphincter at this oxygen percentage, corresponding to

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an altitude of about 30,000 feet. Figure 1 shows a typical response. There was an immediate increase in the tonus, accompanied by an increase in the frequency of the contractions. After about 9 minutes the tone fell off toward normal, and the character of the contractions changed. The contractions became less frequent, but were quite vigorous and prolonged, approaching a condition of spasm. The contractions assumed their normal character only after the anoxemia had been discontinued for about 5 minutes.

The tone of the sphincter was increased in every one of the seven trials at this oxygen percentage, but in two cases the increase was delayed for about 3 minutes after administering the anoxemia. The vigor of the contractions was increased in 4 cases, and diminished in 3.

In every trial the tone of the antrum remained unchanged for about 5 minutes, then rose transiently, and fell to below its normal level. The contractions of the antrum also showed this delayed initial stimulation, with a subsequent depression to a subnormal level. In some instances the contractions were finally completely abolished.

9% OXYGEN

Figure 2 is typical of the results obtained using this degree of anoxemia, which corresponds to an altitude of about 22,000 feet. There was an immediate, marked rise in the tone of the sphincter, followed by a fall to nearly normal after 10 minutes. The height of the contractions of the sphincter was decreased, slightly at first, but still further, concurrent with the fall in tone.

The tone of the antrum fell immediately upon administering the anoxemia. The height of the contractions was at once diminished, and after 12 minutes the contractions practically disappeared.

Eight determinations were made at this percentage. In six cases the tone of the sphincter showed a rise, but this rise was delayed in one case. The height of the contractions of the sphincter was increased in 3 cases, decreased in 4, and unchanged in 1.

About half the determinations on the antrum at this degree of anoxemia showed an immediate fall in tone and contractions, with an abolition of the contractions after about 10 minutes. The other half showed an initial stimulation of both the tone and the contractions, with a subsequent fall of both to below their previous normal level.

14% OXYGEN

This mild degree of anoxemia was administered in two cases, in an attempt to establish a threshold. This oxygen percentage corresponds to an altitude of only about 10,000 feet. Figure 3 is a section of one of the records obtained. The tone of the sphincter remained unchanged for about 3 minutes, and then rose for about an equal period. Concurrent with the rise in tone the frequency of the contractions was increased, and they became more spastic in nature. At the end of 6 minutes the record assumed a normal character.

In the other trial at this oxygen percentage the tone of the sphincter was unchanged, but the vigor of the contractions was increased considerably.

No determinations were made upon the antrum at this degree of anoxemia.

RESUME

Using 6%, 9%, and 14% oxygen, respectively, it was found that the tone of the pyloric sphincter was increased in 14 of 17 trials. The vigor of the contractions of the sphincter was increased in 8 cases, decreased in 8, and unchanged in 1. The antrum showed, in about half the cases, an initial stimulation of tone and contractions, followed by a depression to a subnormal phase. In the other half of the cases the tone and the contractions were initially decreased, and later the contractions were abolished.

DISCUSSION

In the light of previous findings (2) it seems rather surprising that such constant results were obtained on the tone of the sphincter. However, this previous work showed that in the majority of animals anoxemia produced a rise in the tone of the sphincter, and that as a rule, consistent results were obtained with each animal. Since a small number of animals was used in the current experiment it is not so remarkable that a rise in the tone of the sphincter was obtained in 14 of 17 trials. Any increase in pyloric tone, not accompanied by a corresponding increase in the tone of the gastric muscle as a whole, must be considered as a potential factor in delaying gastric emptying. In anoxemia the tone of the gastric muscle tends to be decreased; consequently the increase in pyloric tonus, when it occurs, may be a significant factor in the mechanism of delayed gastric emptying time.

It is interesting to note the inconstancy of the effect of anoxemia on the contractions of the sphincter. In 8 cases they were increased in vigor, in 8 cases they were diminished, and in 1 case they were unchanged. In general, it seemed that if the sphincter was contracting vigorously its contractions would be diminished, and vice versa, so that the effect of the anoxemia seemed to depend upon the previous state of the sphincter.

We realize that 6% and even 9% oxygen represents a rather severe degree of anoxemia. These percentages were used for the sake of ease in interpreting the records, as well as to check on the findings of previous work in which similar percentages were used.

An important part of the present work lies in the fact that significant changes, in both the tone and the contractions of the pyloric sphincter were produced by 14% oxygen. This is a mild degree of anoxemia, corresponding to only about 10,000 feet altitude. In a previous paper (2) it was reported that the threshold for this effect of anoxemia in barbitalized dogs was about 9% or 10% oxygen, and was suggested that a lower threshold might be obtained in unanesthetized animals. The threshold of 14%, herein reported, checks rather closely with the threshold of 15.5% oxygen reported in previous work on gastric emptying time in unanesthetized dogs (1).

It must be noted that anoxemia produces a distinct effect on the pyloric antrum. 6% oxygen caused, after a slight delay, a rise in the tone of the antrum, with a concurrent rise in the height of the contractions. In all these cases the antral contractions were later diminished, and in some instances they disappeared altogether. In attempting to explain the mechanism of the delay in gastric emptying time in anoxemia it has been previously reported (3) that high degrees of anoxemia directly depress the gastric musculature. The findings reported here are in accord with this view.

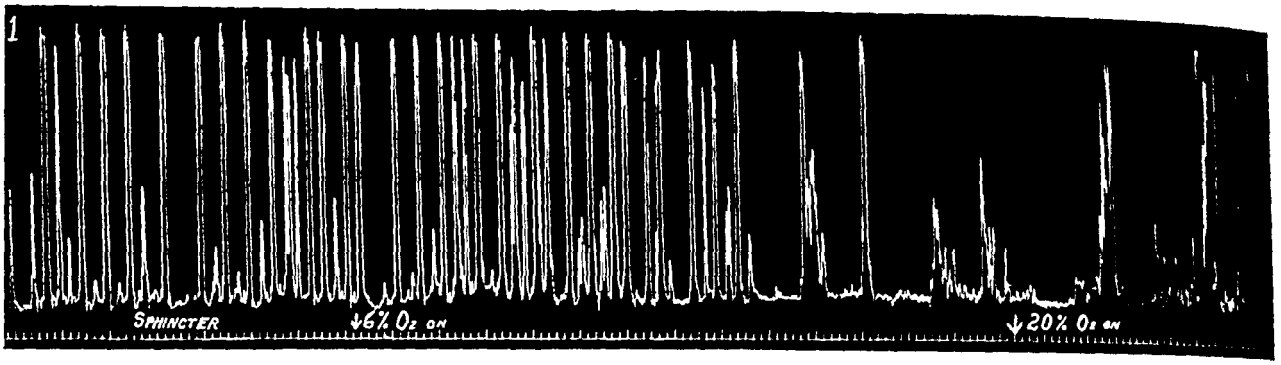


Fig. 1

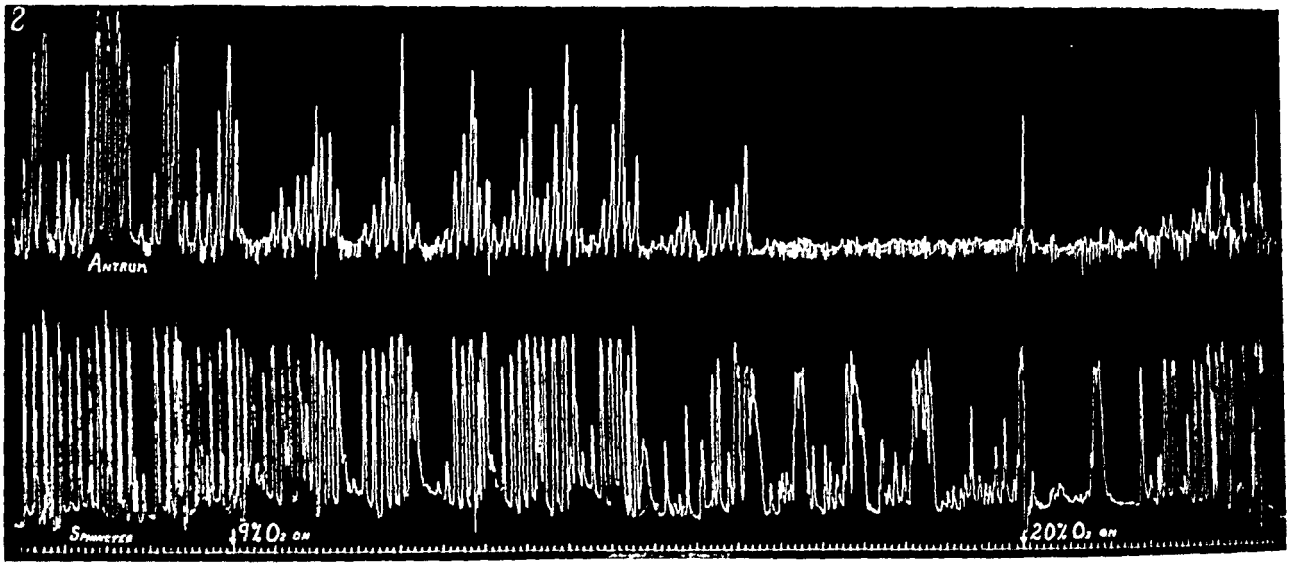


Fig. 2



Fig. 3

Previous reports have further indicated that the pylorospasm produced by anoxemia was on a vagospastic basis (3). The present work would seem to confirm this finding, in so far as certain cases of increased pyloric tonus were accompanied by an initial increase in the motility of the antral musculature. It must be remembered, however, that severe anoxemia, while sometimes transiently increasing antral contractions always decreased antral tone, and ultimately decreased the motility.

It is recognized that there is an increased secretion of epinephrine during anoxemia, probably associated with a general splanchnic stimulation. If so, in view of the vagospasm indicated in previous work, we may in anoxemia be dealing with generalized autonomic excitation. Although the results of such excitation are unpredictable, they could readily include, among other things, such phenomena as we have encountered. In particular, some of the delayed effects on the pylorus could be due to increased adrenal activity. It would be of interest to repeat these experiments on adrenalectomized animals.

It is possible that some of the objective findings of the work here reported may be explained on other bases than those used above. However, in view of the close correlation which seems to exist between this work and previous work mentioned in this paper, the views set forth in this discussion are presented as working hypotheses.

SUMMARY AND CONCLUSIONS

In two unanesthetized animals with permanent fistulae, it was found that anoxemia produced a rise in the tone of the pyloric sphincter in 14 of 17 trials. Reasons are given for including this factor in the mechanism of delayed gastric emptying time during anoxemia. The threshold for this increase in tone was about 14% oxygen. This corresponds to an altitude of about 10,000 feet, and is a rather mild degree of anoxemia.

The change in pyloric contractions was less constant. These were increased in vigor in about half the trials, and decreased in the other half. In general, it seemed that vigorous normal contractions were diminished by anoxemia, and vice versa.

The anoxemia decreased the tone of the pyloric antrum, but in some cases caused an initial increase in the vigor of its contractions. However, these increased contractions were later diminished to below their previous normal level. In most cases the vigor of the contractions was immediately decreased, and the contractions later abolished.

We feel it is possible that these factors, when combined, may be sufficient to account for the delayed gastric emptying seen in anoxemia. Whether or not the pylorus functions as a regulator of gastric emptying under normal circumstances, this work indicates that it may do so under special conditions such as anoxemia. The exact mechanism of the increase in pyloric tonus in anoxemia remains obscure; its further elucidation should shed light on the complex control of the pylorus.

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Studies of Pepsin in Human Gastric Juice*

IV. The Influence of Gastric and Duodenal Disease**

By

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IN the third paper of this series of five (1), we reported studies of the physiologic aspects of secretion of pepsin and gave details as to technic, best method of obtaining juice for study, range of normal values, means and medians, coefficients of variation, effects of age and sex, and so forth.

In this paper we report concentrations of pepsin observed in gastric juice obtained from 1472 men and 374 women, affected with several types of gastric and duodenal disease. We studied also the effects on the secretion of pepsin exerted by successful and unsuccessful operations on the stomachs of 528 persons. The work was done to see if determinations of pepsin in gastric juice are likely to be of any help in the diagnosis of disease.

TECHNIC

For details as to methods used the reader is referred to papers I (2) and III (1) of this series. Suffice it to say

*Studies I and II of this series bore the general title, "Studies of Gastric Pepsin."
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‡Division of Medicine, The Mayo Clinic.
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here that we have used Osterberg's modification of the Gates-Gilman-Cowgill method for measuring pepsin. The unit of pepsin used represents the proteolytic activity of a 1 per cent solution of a 1:10,000 commercial pepsin. We used three types of juice which for the sake of brevity we will call test-meal, fasting, and histamine juice. The first was obtained one hour after the ingestion of eight arrowroot cookies and 400 c.c. of water, the second was removed in the morning before breakfast, and the third was removed in six samples taken at intervals of ten minutes following the injection of a dose of histamine representing 0.1 mg. for each 10 kg. of body weight. A small-bore Sawyer tube was used.

With the first two types of juice we estimated concentrations of pepsin. With histamine juice we obtained also a figure representing quantity of pepsin which we call PV or pepsin-concentration times volume of juice secreted. The particular PV referred to in several places in this paper represents the sum of the quantities of pepsin secreted in each of the first three ten-minute intervals after the injection of the histamine. Studies of the coefficients of variation for secretion of pepsin in the three different types of juice showed that figures representing concentration of pepsin in test meal juice were the least variable and probably therefore the best to use in studies such as the one here reported.

In order to simplify the reporting of all data for pepsin obtained with the three types of juice taken from a group of persons with some particular disease, we have converted figures for concentration of pepsin in fasting juice and for quantity of pepsin secreted in the first thirty minutes after injecting histamine into figures for concentration in test-meal juice, by multiplying by factors of 0.63 and 0.35 respectively. The derivation of these factors was described in paper III of this series (1). We felt safe in combining data in this way not only because we found the numerical relationships between pepsin values in the different juices so constant but because before making Table I, with the combined index, we first studied median and mean values for the three juices separately, and found that, within limits of error of sampling, they were affected in the same way by each disease.

We have depended on the median rather than the mean as an index of central tendency because of the skewness of the distributions. Details in regard to this will be found in paper III (1).

Figures for men and women were so different that they had to be studied separately. We have not attempted to correct the figures for the factor of age. Fortunately, in most of the groups the mean age was about the same.

SECRETION OF PEPSIN IN DISEASE

Duodenal ulcer. As everyone knows, duodenal ulceration is a disease that varies markedly in its severity. Accordingly, we divided our cases, first, into two groups of the quiescent or healed, and the active; and second, the active cases were subdivided into the medical and the surgical depending on the type of treatment advised by the physicians and surgeons who saw the patient. This criterion was used because in most cases this decision as to the type of treatment advisable is based on the severity of the symptoms or the presence of complications.

TABLE I

Concentrations of Pepsin and Acid in Gastric and Duodenal Diseases

	Men						Women					
					Concentration of pepsin						Concentration of pepsin	
	Number of subjects	Mean age	Achlorhydria, incidence in per cent	Mean concentration of acid*	Median†	Probable error†	Number of subjects	Mean age	Achlorhydria, incidence in per cent	Mean concentration of acid*	Median†	Probable error†
Normal	103	43	5	44	148	± 7	140	41	3	35	126	9
Duodenal ulcer, quiescent	100	57	1	49	252	±18	39	48	0	42	188	28
Medical	616	44	0	54	352	±11	183	45	0	47	209	20
Surgical	496	42	1	60	501	±11	74	43	0	51	272	30
Pseudo-ulcer	94	40	3	52	405	33	2[illegible]	45	0	43	125	23
Gastric ulcer	75	49	0	42	253	17	21	44	0	42	135	24
Carcinoma	91	56	33	33	276	15	35	54	40	36	127	19
Gastro-enterostomy without ulcer	70	45	29	39	126	30	17	43	—	—	238	41
Gastro-enterostomy with ulcer	207	47	0	43	212	18	24	41	0	45	136	22
Other operations without ulcer	48	43	33	50	130	37	9	37	—	—	298	37
Other operations with ulcer	140	41	4	59	414	21	13	49	0	35	239	31

*Incidence of achlorhydria in per cent and figures for mean acid are for cases in which test meal was used.
†Figures for pepsin are derived from analyses of test meal, histamine and fasting juice. Values obtained from study of fasting and histamine juice were converted into terms of pepsin in test-meal juice as explained in the text.

Table I shows that the median value, expressed in terms of concentration of pepsin in test-meal juice, rose definitely with the severity of the disease. In the case of men, the three medians of 252, 352, and 501 are to be compared with the median of 148 for normal persons. In the case of women, the corresponding figures were 188, 209, 272, and, for the normal, 126. It is of interest to note that free acidity varied in the same way as did the pepsin, the mean values for healed, medical and surgical ulcers in men being 49, 54, and 60 respectively, as compared with a normal of 44. For women, the corresponding figures for acid were 42, 47, 51, and 35.

In the case of many of the patients with duodenal ulcer who were operated on, the surgeon described the lesion as being acutely inflamed, multiple, or penetrating, or complicated by the presence of duodenitis, gastritis, or a gastric ulcer. On studying the concentra-

tions of pepsin in cases classified under these headings, we found a number of interesting things. For instance, median concentrations of pepsin in cases of duodenal ulcer complicated by gastric ulcer or gastritis were decidedly lower than in cases of simple duodenal ulcer. As will be seen in the next section the median concentration of pepsin in cases of gastric ulcer was only slightly above normal. A possible explanation of this is that inflammation of the gastric mucosa apparently tends to lower the secretion of pepsin and acid, which otherwise might be high. When duodenal ulcer was complicated by duodenitis, the median concentration of pepsin was approximately the same as that observed in the case of the whole group of surgical duodenal ulcers, and in the cases of penetrating and of multiple duodenal ulcers. In patients in whom the ulcer was producing obstruction, there was a high median value of 583 units.

The acuteness of the inflammatory process was reflected in the levels of concentration of pepsin; in those cases in which the ulcer was described as being acutely inflamed the median was 903 units whereas in those in which it was said to be subacutely inflamed, it was 514 units, and in those with a more chronic type of ulcer it was only 483 units.

Curiously in the case of 112 patients who had had one or more hemorrhages and in a group of twenty-six who had suffered with intractable symptoms, the median concentration of pepsin was only 375 units.

Pseudo-ulcer. We use the term "pseudo-ulcer" to describe a syndrome resembling ulcer in patients in whom an ulcer cannot be demonstrated. The patients usually show the same tense, sensitive, nervous make-up which is seen so commonly in persons with true ulcer.

Table I shows that the figure for median concentration of pepsin in men was 405, which lies between those for medical and surgical ulcers. The mean acidity of 52 lies between values for healed and medical ulcers. In our series of twenty women, it is curious that the median figure for pepsin was the same as that of the median of the normal controls; the mean acidity was eight points above normal, corresponding to that for healed ulcers.

It is obvious from this that estimations of the concentrations of pepsin and acid are equally useless to the clinician, who, in these puzzling cases, has to decide whether or not an ulcer is present.

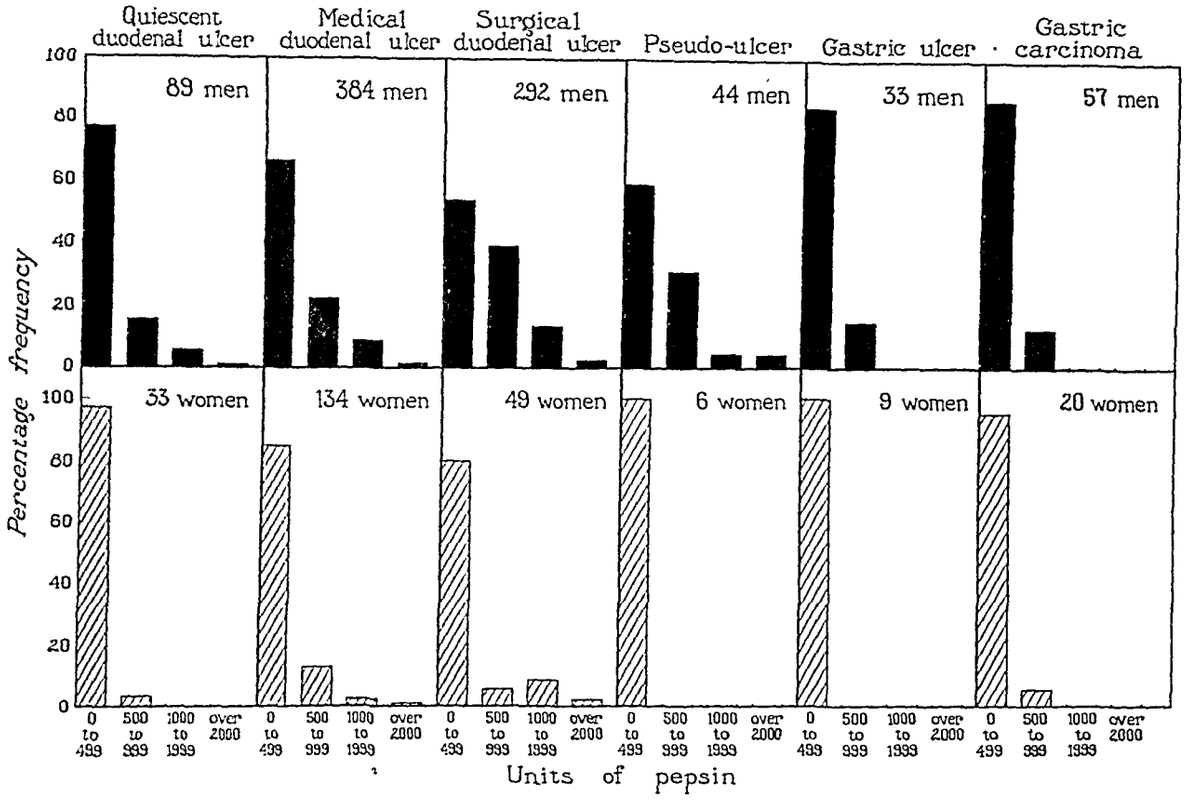


Fig. 1. Percentage distributions of concentrations of pepsin in test-meal juice obtained from men and women with different gastric and duodenal diseases.

Gastric ulcer. In men with gastric ulcer the median concentration of pepsin was 253 units which corresponds with that of healed duodenal ulcer. The mean acidity in this group of seventy-five was that of normal persons. As we have shown in a paper based on the analysis of data from a much larger group of patients, the acidity is usually somewhat reduced below the level of normal.

In a group of twenty-one women with gastric ulcer the median pepsin was about normal and the mean acid was seven points above normal.

Carcinoma of the stomach. The reader must be warned at this point that since, in the case of carcinoma of the stomach, we were most concerned with the problem of diagnosis, which is seldom difficult except when the lesion is small and ulcer-like, most of the persons selected for study were of the type who have considerable free acid in the gastric juice. Sixty-seven per cent of the men and 60 per cent of the women had such free acid, and the respective means for data from these men and women were 33 and 36 units.

It is interesting to note that the men with carcinoma showed a median concentration of pepsin of 276 units which is to be compared with 253 for benign gastric ulcer and 252 for healed duodenal ulcer. In women

the median pepsin was 127 which is almost identical with the normal of 126.

Obviously then, estimations of pepsin cannot contribute anything to the oftentimes difficult problem of differentiating carcinomatous and benign gastric lesions.

The stomach that has been operated upon. It is generally conceded today that a successful gastro-enterostomy lowers gastric acidity. Now we find that in seventy men who returned to report satisfactory results after this operation, the median pepsin value was 126. If we assume that, before operation, these patients had a median pepsin of about 500, such as we find in the cases of Mayo Clinic patients with surgical duodenal ulcer, then we must conclude that the operation reduced the concentration of pepsin to a fourth of its former value, while, at the same time, it reduced the acidity to two-thirds of its presumable former value.

Curiously, in our series of seventeen women with a successful gastro-enterostomy, the figure for median pepsin was only 34 units lower than that for women with surgical ulcer. Still more curious is the fact that in the case of twenty-four women with recurrent ulcer after gastro-enterostomy, the median pepsin value was 136, which is closer to the normal of 126 than to the 272 for surgical ulcer, but with such a small group it is impossible to say whether or not this low figure has any significance.

In the case of 207 men who had submitted to gastro-enterostomy and who returned with symptoms of ulcer, the median pepsin value was 212, which is to be compared with the 126 for a group of patients with successful gastro-enterostomy and the 501 for patients with surgical duodenal ulcer.

Evidently, in the presence of an active ulcer after gastro-enterostomy, the secretion of pepsin is increased much as is the secretion of acid.

There were forty-eight men and nine women who returned after a successful operation on the stomach other than gastro-enterostomy. In most cases this was a pyloroplasty. In men the median pepsin value was practically the same as that seen in cases of successful gastro-enterostomy but in women it was 25 per cent higher.

In the case of the 140 men with unhealed or recurrent ulcer after some gastric operation, other than gastro-enterostomy, the median pepsin value was 414, which is to be compared with the 130 for patients with similar but successful gastric operations and the 212 for patients with an unsatisfactory gastro-enterostomy.

In the case of thirteen women with unsuccessful gastric operations, other than gastro-enterostomy, we found the presence of an ulcer associated with lower concentrations of pepsin. The median of 239 units is to be compared with the 298 units for women with a successful gastric operation other than gastro-enterostomy, and the 136 units for women with an unsuccessful gastro-enterostomy.

Figure 1 shows percentage distributions of concentrations of pepsin in test-meal juice obtained from men and women with the commoner types of gastric and duodenal disease.

CONCLUSIONS

It is obvious from the figures in Table I that the median concentration of pepsin in gastric juice was closely correlated with the severity of the symptoms produced by ulceration in duodenum or stomach. Unfortunately for the clinician, there was so much individual variation in the figures and so much overlapping of distributions representing data from normal calm persons, from highly nervous persons, and from patients with the several diseases, that it is not likely that an estimation of the concentration of pepsin can ever have much diagnostic value. The test fails the physician just where he most needs help, namely in differentiating pseudo-ulcer from duodenal ulcer and malignant from benign gastric ulcer.

In the next paper we shall take up the possible value of determinations of pepsin in detecting the patient with ulcer who is likely to do badly after an operation on the stomach.

SUMMARY

Studies were made of concentrations of pepsin found in the gastric juice of 1937 men and 437 women suffering with several types of gastric and duodenal disease, with or without the modifying influence of a successful or an unsuccessful operation on the stomach.

Concentrations of pepsin were estimated by a modification of the Gates-Gilman-Cowgill method. The median was used as a measure of central tendency.

In cases of duodenal ulcer the concentration of pepsin was considerably higher than normal, and it varied with the severity of the symptoms of the disease and with the degree of acuteness of the inflammatory process.

There was a similar gradation in the acidity of gastric juice obtained from patients with the different types of ulcer but the differences were not so great.

In cases of pseudo-ulcer in men the median pepsin value lay between the figures for cases of medical and surgical duodenal ulcer. In women with pseudo-ulcer the median pepsin did not differ from that of normal controls.

In men with gastric ulcer the median pepsin value was slightly increased; in women it was practically that of the normal controls.

In the case of carcinoma of the stomach data were taken mainly from patients with small lesions and free hydrochloric acid in the gastric juice. In the men the concentration of pepsin was slightly increased to a level about that seen with benign gastric ulcer; in the women there was no change from normal.

In the case of men in whom a gastro-enterostomy had been successful, median concentration of pepsin was normal, which means probably that there had been a drop of about 375 units from the high median value found in patients with surgical ulcer. This drop of 75 per cent is greater than the 34 per cent drop observed in gastric acidity.

In the presence of a recurrent duodenal ulcer or of a jejunal ulcer following gastro-enterostomy, the concentration of pepsin appeared to be increased.

The same type of change was observed when ulceration followed other types of operation on the stomach

or duodenum. In women the groups studied after operations were so small that no positive conclusions could be drawn as to the slight changes observed in the median concentration of pepsin.

Unfortunately the individual variability in pepsin readings is so large, and the overlapping of distributions so great, that estimations of this ferment can seldom have much diagnostic value.

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Studies of Pepsin in Human Gastric Juice*

V. Its Prognostic Value**

By

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IF only the gastro-enterologist could tell in advance which of his patients with ulcer, if sent for surgical treatment, would promptly get well and stay well, and which would soon return with the lesion reactivated or with a new one boring into the jejunum, his life would be much happier, and no longer would he let a small percentage of very bad results restrain him from making use of an operation which, in most cases, works perfectly.

Under the compulsion of this fear, every clinician and surgeon of experience has developed a set of "hunches" which cause him to refuse operation to certain patients, usually the tense, nervous ones with a high gastric acidity. But how many practitioners have taken the time to record their prophecies and then, later, to compare them with what actually happened? Or how many have correlated the degree of gastric acidity found at the time of the first examination with the results obtained after operation?

Because previous studies at this Clinic (1) had shown that there is nothing distinctive about the gastric acidities of the patients who do badly after gastric operations, we were particularly desirous of seeing if analyses of another component of gastric juice, in this case pepsin, would have any better prognostic value. We here report work done to see if there is any correlation between the concentration of pepsin in the gastric juice and the character of the results obtained after operation on the stomach.

TECHNIC

In estimating concentrations of pepsin, we used a modification of the Gilman-Cowgill method, details of which can be found in a paper by Osterberg, Vanzant, and Alvarez, published in 1933 (2). In most cases we used gastric juice withdrawn one hour after the giving of a test meal consisting of eight arrowroot crackers and 400 c.c. of water. When fasting or histamine juice was used, the figures expressing concentration or amount of pepsin were converted into terms of concentration of pepsin in test-meal juice, with the help of factors given in paper III of this series (3). The median was used instead of the mean as an index of central tendency. The figures for concentration of pepsin for men and women were so different that we studied them separately.

RESULTS

In preparing for the analysis here reported we began a few years ago to study cases in which the concentration of pepsin in the gastric juice was known and in which the patient, after an operation on the stomach, returned to this Clinic with recurrent symptoms of ulcer. When we began to write this paper, we had data from thirty-eight such cases in which a diagnosis of "recurrence" had been made after study here. In order to secure data from a control group of persons who had had, first, the necessary study of the gastric juice, second, an operation on the stomach, and third, a good result, we sent out a questionnaire which brought in 238 replies. These answers were segregated into three groups denominated "entirely satisfactory," "slight indigestion," and "possible recurrence."

All the data analyzed in this paper were from patients with duodenal ulcer; we did not find any case of recurrence following operations for the relief of gastric ulcer or combined gastric and duodenal ulcer. Altogether we had data from 233 men and forty-three women. In 162 cases, the operation performed was gastro-enterostomy; in ninety-two, it was pyloroplasty; in twenty-one, it was resection, and in one case, it was a simple excision of the ulcer.

On examining the data we found that, in the case of the 147 men who secured a perfect result, the median pepsin concentration, before operation, was 433 units. This figure stands halfway between the median of 352 for cases of "medical" ulcer and the

*Studies I and II of this series bore the general title, "Studies of Gastric Pepsin."
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median of 501 for cases of "surgical" ulcer, reported by us in paper IV of this series (4). The men who were suffering with symptoms which suggested the presence of a recurrent or new ulceration were found originally to have had a median concentration of 467 units of pepsin, while those men in whose case a definite diagnosis of recurrent or new ulceration was made, had originally a median concentration of 485 units.

Even if we could be sure that these small differences in the median would be maintained if we were to study thousands of cases, the differences are so small and the overlapping of distributions is so great that we must conclude that the concentration of pepsin in an individual must be without prognostic value. Incidentally, it should be noted that in each group the median value was less than 500 units which marks the upper limit of normal.

In the case of the women, the groups were so small that little can be inferred from the differences observed in the median values for pepsin. Curiously, the highest concentrations of pepsin were found in patients who obtained the best results, and the lowest in patients who suffered a recurrence.

CONCLUSIONS

It is obvious from this work that measurements of concentration of pepsin in the gastric juice have no prognostic value.

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SECTION III—*Nutrition*

The Effects on the Gastric Juice of Man of Six Weeks' Deprivation of Vitamin B_1*

By

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SEVERAL years ago, Danysz-Michel and Koskowski (1922) (1) and Farnum (1926) (2) reported a falling off in gastric secretion in animals placed on a diet poor in vitamin B_1. Gildea, Kattwinkel, and Castle (1930) (3), using a similar diet, did not see much change in gastric acidity, and Cowgill and Gilman (1934) (4) had some negative results, but Webster and Armour (1934) (5) and Komarov (1934) (6) reported that the stomachs of their dogs regularly became anacid. This happened usually after the animals had been on the deficient diet for about three weeks, and the gastric mucosa returned to normal within a few days after a complete ration was again supplied.

These results of Webster and Armour and Komarov were so striking that the senior writer of this paper decided that the experiment should be repeated on men and women. Obviously, if this type of dietary deficiency were promptly to produce anacidity in man, the medical profession might find itself in possession of a convenient method of treatment for intractable ulcer. Fortunately for our purpose, experimenters seemed to agree that lack of vitamins other than B_1 had no effect on gastric juice.

Against the hope that food deficient in B_1 might be helpful in cases of ulcer was the fact, reported by several observers (Sure and Thatcher, in 1934 (7), and Dalldorf and Kellogg in 1932 (8)), that such a diet sometimes seems to produce peptic ulcer in rats. Actually, Sure and Thatcher recommended that attempts be made to treat ulcer with a diet rich in vitamin B_1.

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Submitted August 8, 1935.

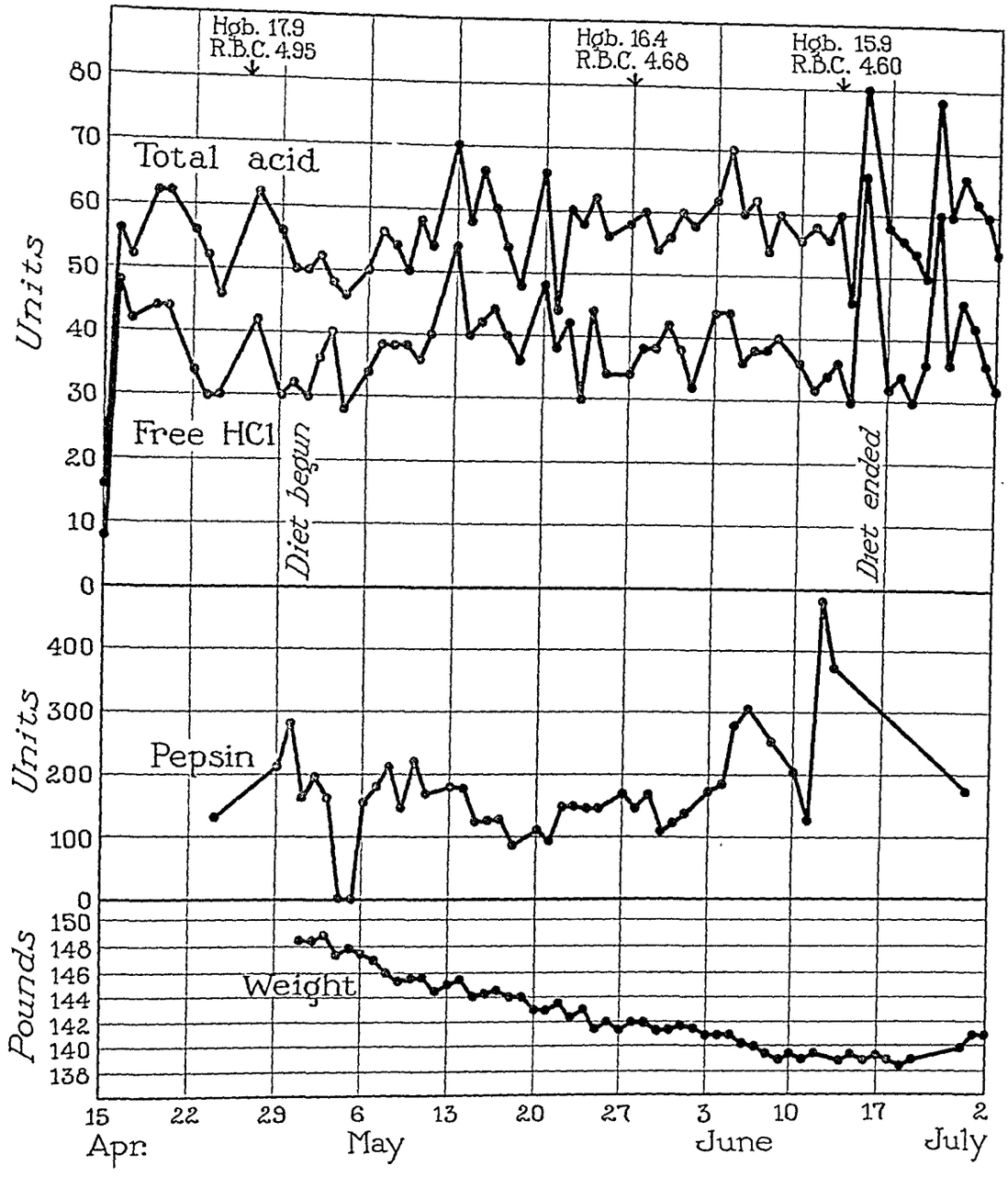


Fig. 1. (Dr. P.). Curves showing daily changes in concentrations of acid and pepsin in the gastric juice, and changes in weight.

After reviewing these contradictory reports of experiments on animals, we turned to the literature on beriberi to see if patients with this disease suffer with anacidity, and again we were puzzled. Kitamura and Shimazono (1912) (9) studied the gastric juice of eighty-seven Japanese soldiers with beriberi and found only about a third with anacidity and subacidity. In most of these cases the disease was severe. Ohta and Izumita (1930) (10) studied children with beriberi and found most of them with an anacid or subacid stomach; a few had normal acidity, and a very few, hyperacidity. Contrary to the experience of the experimenters with dogs, the Japanese physicians found that in the children, gastric acidity returned to normal only after three months of treatment.

In Vedder's monograph (11) on beriberi, we did not find any reference to the incidence of peptic ulcer in patients with this disease, but in a review by Cowgill (1934) (12), we found that Middleton (1914) (13) reported a case of duodenal ulcer complicating beriberi. We haven't access to this paper so we do not know if the beriberi resulted from the use of too restricted a diet in the treatment of ulcer. Sixty-five per cent of Kitamura and Shimazono's sick soldiers were without symptoms of indigestion.

As we were starting our experiment we found the articles by Elsom (1935) (14), who kept two persons for five months on a diet moderately deficient in vitamin B_1. It should be noted that the two persons studied by Elsom were chosen because they had already shown symptoms suggesting the presence of beriberi. In one case, gastric acidity was normal when tested at the end of the period of dietary restriction, and in the other, acid could be obtained only after injecting histamine.

On April 15, 1935, after consultation with G. R. Cowgill and R. M. Wilder, we began the experiment here reported with three volunteers. *Dr. P.*, a man, twenty-nine years of age, was 174 cm. (5 feet 9 inches) in height, and weighed 67.5 kg. (148.5 pounds). His basal metabolic rate (the mean of four tests) was —10% and his ideal weight 69 kg. *Mrs. P.*, twenty-seven years of age, was 169 cm. (5 feet 7 inches) in height, and weighed 50 kg. (110 pounds). Her basal metabolic rate (the mean of four tests) was -7%, and her ideal weight was 63 kg. *Miss S.*, aged forty-five

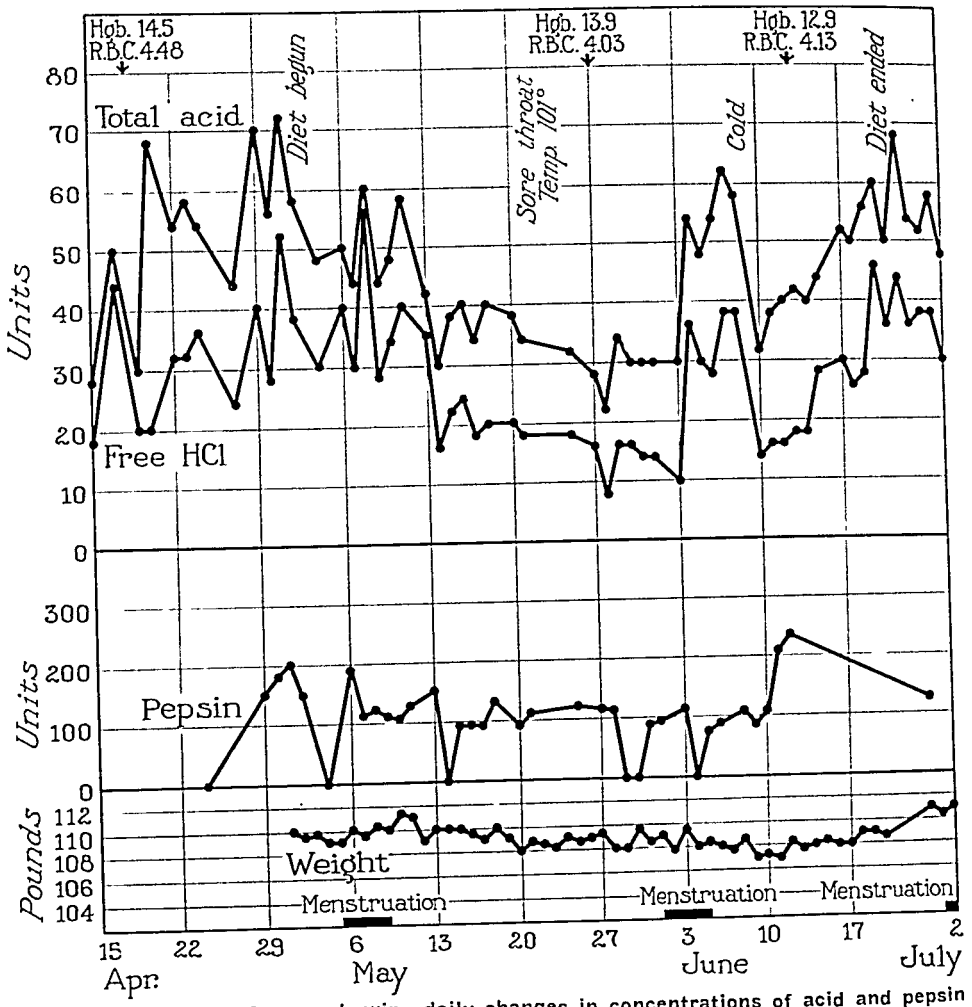


Fig. 2. (Mrs. P.). Curves showing daily changes in concentrations of acid and pepsin in the gastric juice, and changes in weight.

years, was 166 cm. (5 feet 5 inches) in height, and weighed 76 kg. (167.5 pounds). Her basal metabolic rate (average of three tests) was -21%, and her ideal weight was 66 kg. All were interested in medicine and could be depended on not to eat anything but what was prescribed. All three remained at work.

The first two have always enjoyed good health and good digestion; the third suffers with an ulcer-like syndrome but has no demonstrable ulcer in stomach or duodenum.

In prescribing the diet for these three persons we were guided by the standards given in Cowgill's splendid monograph (15) on the vitamin B requirement of man. From his chart number 6, we found that the minimal vitamin/calorie ratio for *Dr. P.* was about 1.85. *Mrs. P.'s* ratio for her actual weight was 1.40 and for her ideal weight, 1.80. *Miss S.'s* ratio for her actual weight was 2.15 and for her ideal weight, 1.85.

For the sake of convenience in calculating and handling the diet all three volunteers were given a diet which supplied 2200 calories and 2687 units of vitamin B_1. This gave a vitamin /calorie ratio of 1.2 which, if maintained for a sufficiently long period, should certainly have resulted in illness. Fortunately, beriberi does not appear until a deficient diet has been consumed for at least three months (Vedder, 1913) (11).

A gastric analysis was made almost every day. *Miss S.* was already well-used to the stomach tube, and the other two soon became accustomed to passing it themselves.

We used the usual test meal employed at The Mayo Clinic consisting of eight arrowroot cookies with 400 c.c. of water. The gastric juice was removed after one hour with the help of a small-caliber Sawyer tube. The acidity was titrated in the usual way with Töpfer's reagent and phenolphthalein. Pepsin was measured with a modification of the Gilman-Cowgill method described by Osterberg, Vanzant, and Alvarez (1933) (16).

The first two weeks of the experiment were spent in establishing base lines of gastric acidity and concentration of pepsin while the volunteers were on a liberal diet. On the first day of May, they began taking all their meals at the Rochester Diet Kitchen where the food, low in vitamin B content, was prepared. At each meal they ate all the food placed before them. The only complaint made came from the two persons who were restricted as to calories; naturally, they were hungry.

Figure 1 summarizes the results of the experiment on *Dr. P.* After the first day, when anxiety probably accounted for the marked subacidity observed, he was found to have a free acidity averaging about 35 units. Soon after he went on the deficient diet the acidity rose to a mean around 42 units, and later it dropped to

about 38 units. During most of the experiment, the concentration of pepsin varied around 150 units, which is normal.

Three days before the end of the experiment, *Dr. P.* was overjoyed to hear that he could soon eat freely again. He had been working hard, eating less than he wanted, losing weight, and suffering somewhat from hunger. Accordingly, when he saw relief on the way, his mind filled with thoughts of food, and he amused himself with plans of the meals he was going to order. Apparently as a result of this there came a sudden upward surge in the concentration of the pepsin in the gastric juice. It rose to a level of 480 units, which is about the upper limit of normal. Three days later, when he began to eat what he pleased, there came a second remarkable rise, this time in the free acid titer of the juice.

Dr. P. lost 9½ pounds (4.3 kg.) during the experiment, most of this being due to the caloric deficiency in the diet. He lost another ½ pound (0.2 kg.) during the five days following the cessation of the experiment, and then he gained 3 pounds (1.4 kg.) A month later, he had not gained any more of the lost weight, but this may have been due to the fact that he has seldom gained during the heat of summer.

Except for hunger, *Dr. P.* felt well throughout the period of the experiment. He felt tired during the last week, but this may have been due to overwork.

We cannot see any evidence from this experiment of a deleterious effect of the deficient diet on gastric acidity; if anything, the acidity was slightly raised. The concentration of pepsin in the gastric juice was also unaffected.

The record of *Mrs. P.* is very interesting (Fig. 2). She began with a free acidity of about 32 units, with limits of 20 and 52 units. On May 14, after she had been living on the deficient diet for two weeks, the free acidity fell suddenly to around 15 units, where it tended to remain. A week later, on May 21, much soreness of the throat appeared, with general malaise and a temperature of 101° F. She was in bed three days but kept to the diet. The free acidity continued to fall and, on May 28, it was only 8 units. Suddenly, on June 3, the acidity increased to 36 units and remained high for four days, until she again became indisposed, this time with an ordinary cold. Two days later, the free acidity was 14 units. It then climbed steadily until June 20, when it was 46 units, and the experiment was terminated. During the next twelve days, while *Mrs. P.* ate what she pleased, the trend of the gastric acidity was downward.

The impression gained is that, in this case, a deficient diet plus a sore throat or a cold greatly lowered the acidity. It seems probable that the sudden drop in acidity which took place a week before the throat became sore was due to the entrance of the infectious agent into the body. The sore throat was one of the most severe *Mrs. P.* had ever had. Curiously it did not produce enough immunity to protect her against the coming of the coryza; and curiously also, the coryza was not associated with any prodromal drop in acidity. Furthermore, so far as the acidity is concerned, recovery took place differently with the two infections. Since *Mrs. P. had not had a cold in nine* years, she may well be right when she suggests that the deficient diet probably lowered her resistance to respiratory infections. It is interesting to note that the concentration of pepsin was not affected either by the diet or the infections.

The question next arises: Do colds usually reduce gastric acidity in persons living on a normal diet? So far as we have gone, the evidence is against this assumption. In one young woman with functional indigestion and 20 units of free hydrochloric acid in the stomach, an analysis made when she had a cold showed 34 units. Similarly, in a young man with what appeared to be chronic mesenteric lymphadenitis, a gastric analysis made when he was feeling well showed 20 units of free hydrochloric acid; later, when he had a bad cold, there were 42 units, and still later, when he had an acute flare-up of his abdominal infection with a leukocytosis of 18,600 cells, there were 32 units of free acid in the stomach. Another young man with chronic headache and 40 units of free acid had 16 units four days later when he came down with a cold. A middle-aged woman, examined when she had a severe cold, had 20 units of free acid, which is not necessarily abnormal. Unfortunately, in this case, we could not get a control reading when she was well. The work of Vanzant (1931, 1932) (17, 18) and others showed that fever will reduce gastric acidity both in animals and man. Our impression is that the marked and sudden drops in acidity seen with respiratory infections in the case of *Mrs. P.* were due partly to the defective diet.

Mrs. P. gained 1 pound (0.5 kg.) during the first ten days on the deficient diet; later she lost 4 pounds (1.8 kg.), but she gained 2 pounds (0.9 kg.) before she began eating as she pleased. Except for the colds, she felt well throughout the experiment and had a good appetite. This is interesting because it is often said that the first result of eating food deficient in B_1 is loss of appetite.

As a subject for this experiment *Miss S.* had the advantage that her gastric acidity was often abnormally high, and she suffered at times with an ulcer-like syndrome. We hoped, therefore, to see what the diet could do for a person with an "ulcer constitution." Disadvantageous was the fact that she was nervous, temperamental and impressionable. This was reflected even in the figures for the basal metabolic rate. While there was almost no variation in the results of the two series of four tests each, made on *Dr. and Mrs. P.*, the results in the case of *Miss S.* were -27, -21, and -16%. Judging from Figure 3, the emotional instability was reflected much more in the curve representing concentration of pepsin than in that representing acidity.

It is hard to tell anything about the result of the experiment with *Miss S.* because she was so distressed and upset from the moment she went on the deficient diet that in two weeks she had to give up and go back to her usual ways of eating. It is conceivable that the low reading for free acid of 18 points, observed three days after she went back on a full diet, was due to the temporary lack of vitamin B_1, but this is improbable since the acidity fell to the same low level a month later when she was on a normal diet.

It may be worth noting that each of the three dips in the curve of free acidity appeared from nine to eleven days before the beginning of menstruation. In the case of *Mrs. P.* and the two women previously studied by Vanzant and Alvarez (1931) (19), the men-

to produce anemia. Some experiments by Strauss and Castle (1932) (22) suggested that part of the vitamin B complex may have something to do with pernicious anemia. Remissions were obtained in this disease by giving several types of extracts containing vitamin B.

In the cases of *Dr. and Mrs. P.*, the loss of hemoglobin was more marked than the loss of erythrocytes. Thus *Dr. P.* lost 11 per cent of his hemoglobin and 7 per cent of his erythrocytes; *Mrs. P.* lost 11 per cent of her hemoglobin and 8 per cent of her erythrocytes, and *Miss S.* in about thirteen weeks lost 11 per cent of her hemoglobin and gained 7 per cent in the number of erythrocytes.

Careful calculations of the iron content of the diet given the three volunteers shows that it approximated Sherman's standards for minimal requirements. It contained 0.0093 gm. as compared with the 0.010 gm. of the standard. From this it does not look as if the rapid fall in hemoglobin could have been due to a lack of iron. In view of the experience with beriberi, it is hard to blame it on the lack of vitamin B_1, and it is hard to say why the body continued to lose hemoglobin after it was supplied with a normal diet. No yeast or other rich source of vitamin B_1 was given during the period of recovery. It may be that the loss of hemoglobin came because the deprivation of vitamin B_1 was more severe than that observed even in an Oriental prison camp.

SUMMARY

Two persons were maintained for six weeks and one was maintained for two weeks on a diet markedly deficient in vitamin B_1. The vitamin/calorie ratio was 1.2 instead of the minimum of about 1.8, required on the basis of Cowgill's standard.

The concentrations of hydrochloric acid and pepsin in the gastric juice were measured almost every day. In two of the subjects of the experiment there were no definite changes in the gastric juice, and in the third the only changes consisted in two falls in acidity, each associated with a respiratory infection.

The two persons who continued with the experiment for six weeks felt well and enjoyed a good appetite; in fact, one was uncomfortably hungry the whole time. The third person was so apprehensive and upset from the start that in her case no conclusion can be drawn as to the effect of the diet.

The most striking change observed in all three persons was in the hemoglobin content of the blood. In all three persons, this fell off 11 per cent, while at the same time there was a drop of 7 or 8 per cent in the erythrocyte count. In the case of the man these losses were rapidly regained after the return to a normal diet. In the women recovery was slower. The loss of hemoglobin can hardly be ascribed to a deficiency in the iron content of the diet because the deviation from the minimal standard was so slight.

In the case of one of the women studied, menstruation did not seem to have any effect on the concentrations of acid or pepsin in the gastric juice. In the case of the other woman, it may be significant that the three lowest points on the curve representing acidity each preceded by about eleven days the beginning of menstruation.

The work here reported indicates that a diet deficient in vitamin B_1, by itself, is not likely to produce much reduction in gastric acidity. It is possible, however, that such a diet might reinforce the lowering effect on gastric acidity of fever induced by injections of foreign protein.

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The work here reported seems to show that a diet deficient in vitamin B_1 by itself, is not likely to produce much reduction in gastric acidity. It is possible, however, that such a diet might [illegible] effect on gastric acidity of [illegible] of foreign protein.

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SECTION IV—*Roentgenology*

Roentgenographic Studies of the Mucous Membrane of the Colon

I. The Normal Pattern

By

FRANZ J. LUST, M.D.

and

HARRY G. JACOBI, M.D.

NEW YORK, NEW YORK

DETAIL studies of the inner surface of the colon are rather difficult to obtain. Even more difficult however, is the interpretation of these mucosal patterns. A more generalized knowledge of this subject would certainly open up a large field of valuable information and help materially in the diagnosis of colonic lesions. This subject has not received, in this country, the attention that it merits. Abroad, such men as Kalkbrenner (1), Knothe (2) and Berg (3), have all utilized this method a great deal.

In order to appreciate fully the detailed musocal

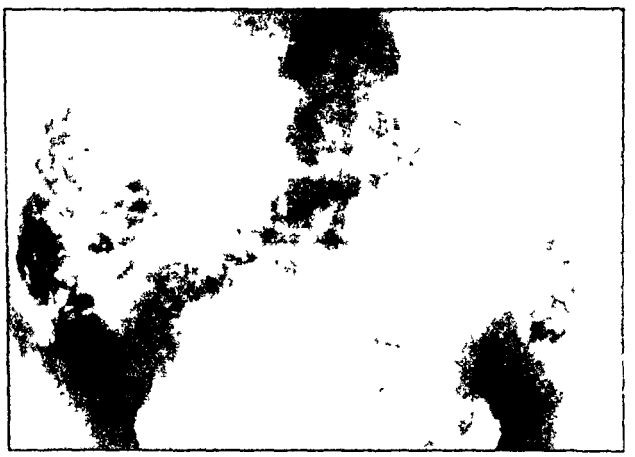


Fig. 1. General mucosal detail of colon obtained by use of our technique.

pattern which we are about to describe, it becomes necessary to sketch briefly the anatomical structure of this mucous membrane together with its physiological action.

The large bowel contains the mucosa, muscularis mucosae, submucosa, the muscularis propria, and the serosa. The mucosal folds which are observed in the colon, during different stages of activity, are not part of the permanent structure or pattern, but are the result of the so-called "plastic" action. The mucosal folds thus formed in this "plastic" action contain mucosa, muscularis mucosae and the submucosa. It is the roentgenographic reproduction of these folds by means of a thin layer of opaque material, which constitutes the main objective of this method. The very richly developed nerve fibres, in the form of Meissner's plexus and the ganglia of the muscularis mucosae, constitutes the local nerve apparatus which determines and controls this pattern formation. The muscularis propria by means of its circular and longitudinal fibres, plays an important part in regulating the calibre of the colon. By its action, alternating pressure and suction effects are created, producing a pumping effect. This acts as a regulatory mechanism for the movement of the colonic contents.

The bulk of the fluid contents of the colon also influences the mucosal pattern. The greater the amount of the contents, the more distended the viscus becomes and as a result, less of the mucosal detail is obtained. With the emptying of the colon, the reverse process takes place with the result that instead of visualizing only the edges of the gut, the actual details of the mucosal folds are obtained. Similarly when barium is introduced into the colon, moderately distending it, very little mucosal detail is possible. The success of the method here employed depends therefore upon the retention of only small amounts of the opaque mixture remaining in the colon, after the greater part of the opaque enema has been evacuated.

The normal mucous membrane relief of the various parts of the colon, reveals a more or less characteristic pattern formation and it is only by clearly understanding these normal appearances, that structural defects in the lining of the large gut, can be detected. In reality, however, the changes which are observed and reproduced are records of changes in the elasticity of the colon. This inherent elasticity is very sensitive to pathological processes which either by pressure or traction on the viscus, alter the normal musocal pattern.

PROCEDURE

The chief objective is to obtain an ideal distribution of the contrast substance throughout the colon, in as evenly a layer as possible. This layer must be so thin

Submitted January 17, 1928.

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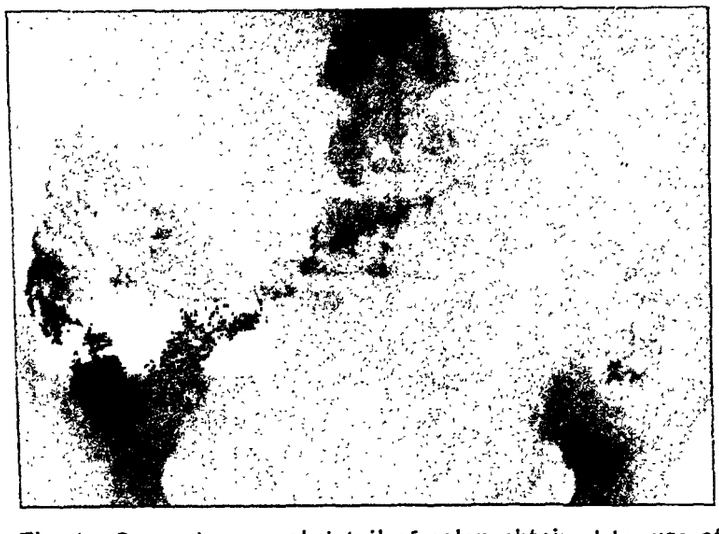


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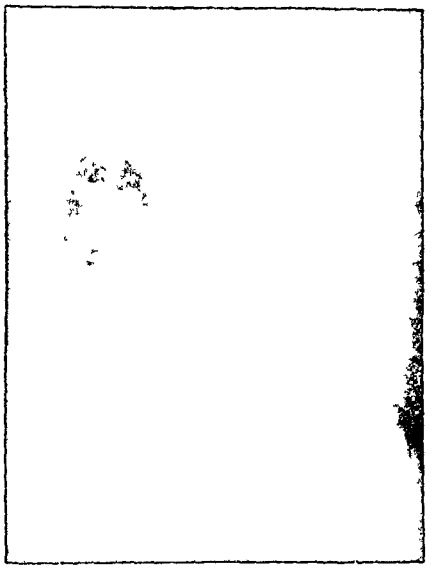


Fig. 4. Descending Colon showing the "parallel lines" arrangement of the mucosal folds.

REPORT OF STUDIES

Roengenographically, the structure of the mucosal pattern of the colon appears as different forms and arrangements of alternating longitudinal and transverse folds. The transverse folds undergo a constant decrease in size as the terminal end of the colon is approached. As a result of this a different picture is imparted to the various portions of the colon.

Fig. 1: Shows the general effect which is usually obtained by following the above mentioned technique. On careful examination the general mucosal pattern of the different parts of the colon may be noted.

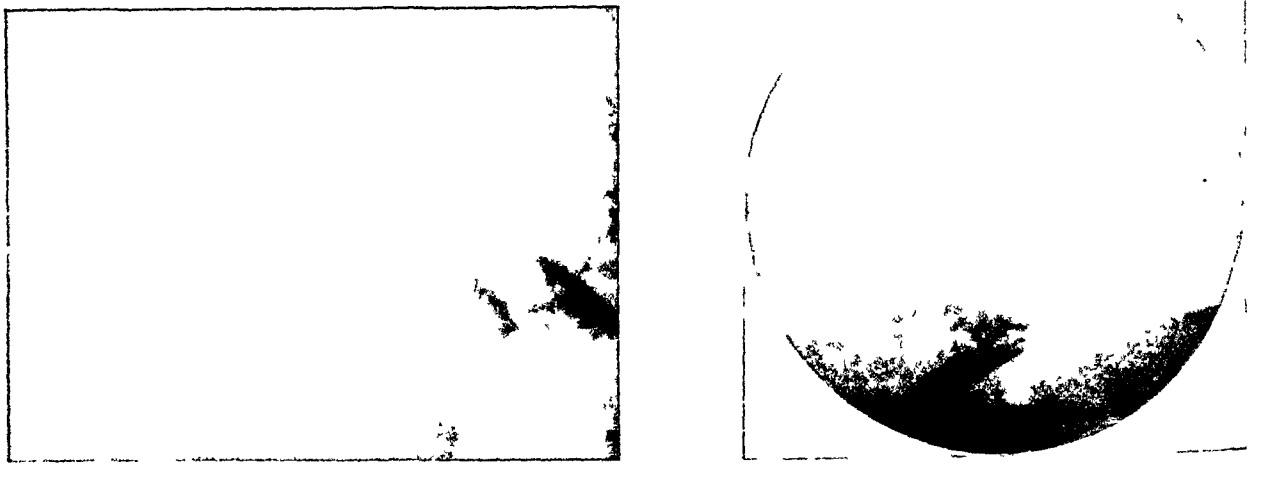
In the cecum, we find that the transverse folds are quite prominent and heavy and appear in a great variety of forms and combinations. As a result of this the transverse rugae can be seen running in different directions and at various angles to the axis of the cecum. This appearance constitutes the so-called usual mucosal pattern seen in the cecum. Fig. 2 shows this arrangement of transverse rugae in greater detail and when this picture is obtained, it is to be considered as fairly characteristic of the normal mucosal pattern of the cecum.

Fig. 3: Shows the mucosal pattern seen in the transverse colon. The main features observed in this portion of the colon may be summed up briefly as follows: (1) There is a marked uniformity of appearance noted throughout this entire region. (2) A decrease in the size of the transverse rugae occurs as compared with those of the cecum. (3) An increase takes place in the size of the longitudinal rugae. There is produced as a result of the above changes an arrangement of the rugae into alternating groups of transverse and longitudinal folds. The so-called haustral units are here seen as consisting usually of three transverse and the same number of longitudinal rugae. This formation can be seen particularly well in Fig. 3A. In most cases anywhere from two to four transverse folds usually alternate with an equal number of longitudinal folds. Sometimes, however, the axes of the transverse rugae appear somewhat distorted, resulting in a Y shaped or chain effect of the mucosal pattern, similar to that seen in Fig. 3B.

In the descending colon, the pattern again shows a change in the structural picture due principally to the diminished size of the transverse rugae. Usually, the transverse folds are so faint that the longitudinal rugae alone are visible. As a result of this there is imparted to the picture the appearance of a series of "parallel lines" which resemble very much that of railroad tracks. Fig. 4 demonstrates this arrangement very well.

In the region of the sigmoid the rugae are found to be much broader, and are mostly Y shaped in their arrangement. Fig. 5 shows the mucosal pattern seen in upper and lower sigmoid.

Sometimes a picture is seen similar to that in Fig. 6, where the mucosal pattern while having the usual form, becomes more or less disrupted or broken up in its outline. The normal general appearance however, is still retained. Some authors (Knothe) have interpreted such an appearance as being due to some form of irritation of the colon. Up to the present time



5 A 5 B

Fig. 5. A—Mucosal pattern of upper sigmoid. B—Mucosal pattern of lower sigmoid.

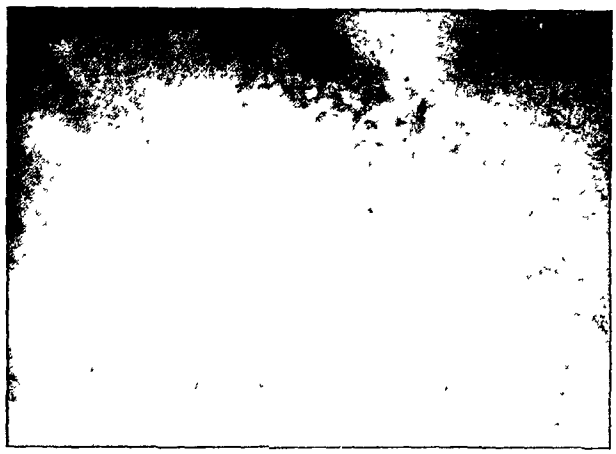


Fig. 6. Disrupted or "broken line" effect of mucosal pattern.

however, we have not become sufficiently convinced of this, and feel that this irregularity or interruption in the outline is nothing more than a variation of the normal picture and of no particular significance. It has therefore been so included in this report.

It must be emphasized that the careful study of the individual folds is just as important as that of the whole pattern. Normally the individual folds are clear cut, nearly straight with no irregularity in the outline. Any interruption in the regularity of the outline, is the result of pathological lesions.

DISCUSSION

The present work is based upon the studies of such pioneers in colon visualization as Forssell (4), Bergand Kalkbrenner (1), and Knothe (2). The investigations of the latter contain by far the more extensive and detailed study of the subject. In his work, Knothe also made use of the simple barium suspension, a method quite similar to ours'. Kalkbrenner recommended a thorium preparation as a contrast substance. Many other studies along these lines have been reported by several European investigators, (5), (6), (7). Our literature however, is quite lacking in the discussion of this excellent and helpful method.

There are several distinct advantages which this method has over that of the ordinary routine procedure which is at present in use in this country. (1) There is a marked reduction obtained in the so-called exaggerated redundancy of the colon with its consequent overlapping of intestinal loops. (2) The actual mucosal surface of the colon is visualized instead of the edges or borders of the gut. (3) The displacement and distortion of the flexures which invariably results from complete filling of the colon with barium or air is eliminated. (4) This method enables us to study more accurately the degree of contraction and elasticity of the colon wall. (5) Careful analysis of the altered appearances of the mucous membrane pattern is more clearly demonstrated due to changes in the normal elasticity of the colon wall. Such changes in the elasticity of the colon wall are chiefly due to pathological processes and can be most admirably demonstrated by this method.

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SECTION V—*Therapeutics*

Aluminum Hydroxide as an Antacid in Peptic Ulcer*

By

W. LLOYD ADAMS, Ph.D.†
I. H. EINSEL, M.D.
and
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THE USE OF aluminum hydroxide in the treatment of peptic ulcer was introduced in Europe over ten years ago. In 1922 Roch (1) reported that "Colloidal hydrate of aluminum absorbs hydrochloric acid. It has proven in our hands the antacid medicament par excellence, quite superior to bicarbonate of soda, magnesia, subnitrate of bismuth, etc." Practically all reports up to the present time deal with the results obtained with proprietary preparations of colloidal aluminum hydroxide. Guillermin (2) called attention to the advantages of this drug over the other antacids, and Kagan (3) in listing its advantages states that "It absorbs excess of hydrochloric acid from the stomach, the acid-containing mass passing through into the intestines and finally being evacuated from the lower bowel. Colloidal hydrate of aluminum, therefore, actually removes from the system the causative acid radical (Cl) instead of temporarily neutralizing it." In 1929 Crohn (4) reported that a colloidal aluminum hydroxide reduced the emptying time of the stomach, lowered the gastric acidity and was devoid of deleterious side effects. Two years later Kreis (5) reported that the drug acted satisfactorily as an antacid, relieved pain, was efficient in small doses, and provided a protective coating to the ulcer surface.

This report presents data which have been obtained at the Cleveland City Hospital on patients suffering from chronic peptic ulcer who have received aluminum hydroxide medicament. Several clinical reports have been given since the introduction of this therapy at the Hospital in 1929 by one of the authors (E), one of them quite recently (6).

A group of twenty-five peptic ulcer patients comprised the first study (7). At that time powdered aluminum hydroxide (Merck and Mallinckrodt) was administered, one-half hour after meals, in doses of 4 grams in water. Observations were made on the acid-base balance of the plasma and on the aluminum content of the blood and the urine. Eleven complete acid-base balance studies were made on four patients, but no changes were noted which could be attributed to the therapy. Table I gives the findings on the aluminum content of the blood and urine in this series of six cases. The data appear to suggest a slight in-

TABLE I

*Aluminum Content of Blood and Urine After Ingestion of Al (OH)$_3$ in Four Equal Doses Daily**

Case	Days of Treatment	Blood Al mg. per 100 gm.	Urine Al mg. per 24 hr.	Al (OH)$_3$ Daily gm.
1. M. K.	0	0.18	0.30	
	2	0.05	0.59	16
	10	0.27	0.88	32
	17	0.24	0.81	16
	24	0.27	0.72	16
	42	0.19	——	16
2. W. J.	0	0.18	0.29	
	10	0.23	0.68	16
	18	0.36	0.66	32
3. R. E.	0	0.12	——	
	21	0.25	——	16
	49	0.13	——	16
4. D. W.	0	0.30	0.17	
	7	0.22	0.43	16
5. H. H.	0	0.23	0.65	
	7	0.42	0.38	16
	14	0.33	0.41	32
6. P. S.	10	0.32	——	
	28	0.22	0.81	32
M. Normal	0	——	0.30	None
R. Normal	0	——	0.53	None
B. Normal	0	——	0.81	None
M. Normal	0	——	0.53	None

*We are indebted to Dr. J. W. Mull for these analyses.

crease in the excretion of aluminum in the urine after its ingestion. However, it must be borne in mind that the amount of aluminum in any case is very small (fraction of a milligram) and it is doubtful if any interpretation can be placed upon the figures other than that the amount of aluminum normally present in human blood and urine is very small and that this is not significantly altered even after large oral doses of Al(OH)$_3$. The method employed for these aluminum estimations was the colorimetric aurin method de-

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*The data presented in this paper are taken from the dissertation submitted by W. Lloyd Adams to the Graduate School of Western Reserve University, June 1933, in partial fulfillment of the requirements of the degree of Doctor of Philosophy.
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Submitted January 15, 1935

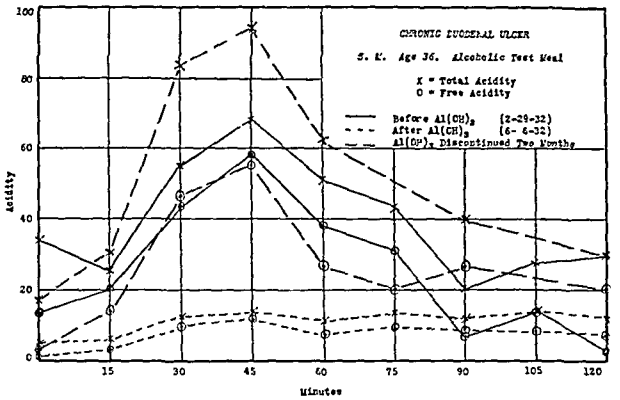


Fig. 1. Gastric acidity before and after receiving treatment of 1 dram $Al(OH)_3$ six times daily and one-half hour after meals (Colloidal $Al(OH)_3$).

scribed by Myers and Mull (8). It is probable that these figures are slightly too high, since Dr. Eveleth obtained an average of 0.076 mg. Al per 100 gm. for ten later blood analyses and 0.104 mg. Al in one 24 hr. urine specimen when traces of iron were removed by extraction in the form of ferric thiocyanate (6).

Inasmuch as relief was so rapid after beginning the treatment of chronic ulcer, it was assumed that the aluminum hydroxide powder neutralized the gastric acidity. Much to our surprise the powder was found to have practically no neutralizing power to HCl in vitro. This fact, and because of its easier administration, led to the preparation of a colloidal cream of aluminum hydroxide. Results with this preparation have been even more satisfactory than those obtained when the powder was used. The improvement may lie in the high neutralizing power of the cream: one c.c. of the cream neutralizes 20 c.c. of 0.1 N/HCl in a period of 4 hours. The neutralization is characterized by an initial rapid partial neutralization followed by a slow reaction until the end-point is reached.

Einsel and Rowland (9) reported unusual success in treating 13 ulcer patients with this colloidal aluminum hydroxide given in doses of 4 cc. six times per day one-half hour after meals. Even refractory cases, which had been treated with soluble alkalies for many months without improvement, responded immediately to this drug.

The study of the effect of aluminum hydroxide cream on the gastric acidity was begun with fractional analysis of the gastric juice after alcohol stimulation. Fifty cc. of 7 per cent alcohol were introduced into the fasting stomach and samples of the contents withdrawn at 15 minute intervals. Figs. 1-3 disclose that prolonged ingestion of aluminum hydroxide cream led to a marked diminution of the gastric acidity. Fig. 1 also shows that reduction of the dosage of the cream is followed by a rise in the acidity. Fig. 4 represents the acid picture in gastric analysis using Bloomfield's technique with histamine as a stimulant. Here, too, the acidity is found to be lowered after a period of aluminum hydroxide cream ingestion.

Up to this time it had been ascertained that the cream was peculiarly efficient in the relief of ulcer symptoms, that prolonged ingestion of the cream did not appreciably affect the aluminum content of the blood or its excretion by way of the urine, that no acid-base balance disturbance was apparent, and that continued ingestion of the cream was followed by a marked lowering of the acid curve of gastric acidity. The indications of Figs. 1-4 were responsible for the intense study of seven typical cases with special reference to gastric acidity and to acid-base balance of the blood. Data for five of these cases are given in Tables II and III below.

EXPERIMENTAL PROCEDURES

No food or liquid was given to the subject between the evening meal and the time of the gastric analysis the following morning. At approximately 8:30 A. M. the following procedures were carried out on all cases.

Unoxalated sample of blood from the median basilic vein was collected under oil without stasis, according to the technique of Myers and Muntwyler (10). A Rehfuss tube was then passed to the most dependent portion of the stomach and the entire contents of the fasting stomach withdrawn. The subject was urged not to swallow saliva and a pan was provided for expectoration. The entire gastric secretion was thereafter collected, by continuous aspiration, in 15 minute periods.

One-half hour after the withdrawal of the fasting contents (end of the second 15 minute period) 0.1 mg. of histamine per 10 kilograms of body weight was injected intramuscularly into the deltoid muscle. One hour after withdrawal of the first sample of blood (end of the fourth 15 minute period) another sample was drawn as before. Two or three 15 minute samples were aspirated after the last blood specimen was taken. Record was made of the volume and of the appearance of blood, bile and abnormal amounts of mucus in all gastric samples.

Each blood specimen was placed in a refrigerator immediately after collection until it could be transported to the laboratory. It was centrifuged at the end of the procedure on the Ward.

When necessary, the gastric samples were filtered through glass wool. Ten cc. of gastric juice were titrated with exactly 0.1 normal NaOH to the salmon pink color of dimethylaminoazobenzene. Duplicate chloride determinations on each gastric sample were made on 1 cc. of sample, using the Wilson and Ball (11) technique. The total base of each gastric sample was determined in duplicate by use of the method of Stadie and Ross (12), although after its publication, the simpler technique of Wright and Allison (13) was followed. The removal of phosphates was found to be unnecessary because of their low concentration in gastric juice collected under these conditions. In normal individuals the phosphorus content of the gastric juice was found by Helmer, Fouts and Zerfas (14) to be below 0.15 mg. per c.c. This is below the limit of interference according to Stadie and Ross. The totals for the 1½ hour period of the gastric analyses, half hour before and one hour after histamine, are recorded in Table II for the volume

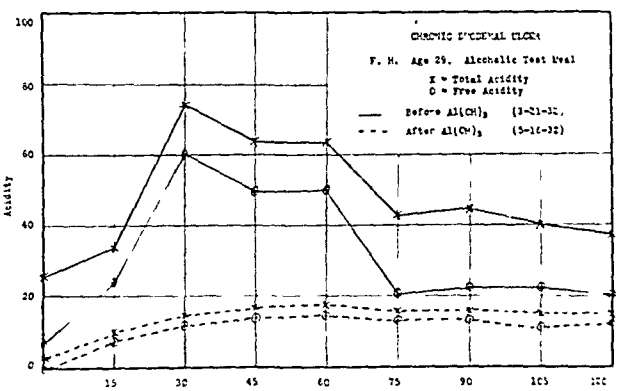


Fig. 2. Gastric acidity before and after receiving treatment of 1 dram Colloidal $Al(OH)_3$ six times per day after meals.

of gastric secretion and the free acidity, total acidity, total chloride and total base. The volume of the residuum is not included in the total volume.

After the blood samples had clotted and had been centrifuged, the serum was removed under oil and placed in a separate container. The carbon dioxide content of each sample was determined by the Van Slyke method (15), usually in duplicate. Chloride and total base determinations of the serum were carried out as mentioned above in the case of gastric analysis. Blood samples were taken for each set of gastric analyses, as the dates in Table III will show, the first being a control and the second, at the

TABLE II

Gastric Analyses Following Histamine Injection in Patients Receiving $Al(OH)_3$ Therapy

Case Date	Specimen Min.	Vol. c.c.	Free Acidity c.c. 0.1 N Conc. per 100 c.c.	Free Acidity Total per Spec.	Total Acidity c.c. 0.1 N Conc. per 100 c.c.	Total Acidity Total per Spec.	Total Chloride m. Eq. Conc. per 1000 c.c.	Total Chloride Total per Spec. x 10	Total Base m. Eq. Conc. per 1000 c.c.	Total Base Total per Spec. x 10	Condition of the sample
I. H. V.	Res.	200									
11-28-32*	15	100	82.5	82.5	94.0	94.0	124	124	36	36	sm. amt. bile
	30	50	102.5	51.2	112.5	56.2	133	66	21	10	normal
	45	100	119.0	119.0	128.5	128.5	149	149	21	21	normal
	60	85	125.0	106.2	135.0	114.7	155	132	21	18	normal
	75	100	122.0	122.0	133.0	133.0	153	153	18	18	normal
	90	55	104.0	37.2	117.5	64.6	142	78	21	12	normal
	Totals	490		538		591		702		115	
11-30-32*	Res.	50									
	15	60	71.0	42.6	84.0	50.4	125	75	43	38	sm. amt. bile
	30	60	60.0	36.0	74.0	44.4	127	76	53	32	sm. amt. bile
	45	75	105.0	78.7	114.0	85.0	150	112	35	26	normal
	60	50	127.0	63.0	133.0	66.0	160	80	18	9	normal
	75	50	121.0	61.0	131.0	65.0	157	78	23	11	normal
	90	70	94.0	65.0	110.0	77.0	142	99	28	20	sm. amt. bile
	Totals	365		346		388		520		136	
12-5-32	Res.	65									
	15	30	59.0	17.7	67.0	20.1	119	36	48	14	sm. amt. bile
	30	30	50.0	15.0	62.0	18.6	114	34	48	14	normal
	45	77	72.0	55.4	80.5	61.9	137	106	55	43	normal
	60	37	107.0	39.6	119.0	44.0	158	58	29	11	normal
	75	51	119.5	60.8	129.0	65.8	161	82	20	10	sm. amt. bile
	90	57	101.5	57.6	112.0	63.8	152	86	21	12	normal
	Totals	282		246		274		402		104	
12-7-32	Res.	58									
	15	60	62.5	37.5	79.5	48.7	124	74	41	25	sm. amt. bile
	30	64	37.5	24.0	49.5	32.6	106	68	51	32	normal
	45	70	91.0	63.9	98.0	68.2	137	96	34	24	sl. red tinge
	60	43	106.0	45.8	115.0	49.7	149	64	23	10	sm. amt. bile
	75	61	115.5	70.4	124.0	75.6	152	93	22	13	sm. amt. bile
	90	50	99.2	49.6	110.0	55.0	143	72	30	15	sm. amt. bile
	Totals	348		291		330		467		119	
12-12-32	Res.	80									
	15	40	63.6	25.4	78.0	31.2	122	49	51	20	normal; sl. red
	30	32	56.2	17.8	68.5	21.7	109	35			normal; sl. red
	45	90	94.0	85.6	104.0	93.6	136	122	33	30	normal; sl. red
	60	73	121.5	88.6	127.5	93.0	156	114	28	21	normal; sl. red
	75	50	119.0	59.3	126.5	63.2	148	74	24	12	normal; sl. red
	90	41	110.0	45.2	118.7	48.3	140	57	24	10	normal; sl. red
	Totals	326		322		351		451			
1-18-33	Res.	100									
	15	45	73.5	33.0	82.3	37.0	113	51	36	16	sm. amt. bile
	30	43	64.0	27.3	74.5	32.0	108	46	34	14	normal
	45	46	82.0	37.7	90.7	41.7	124	57	36	16	normal
	60	75	113.0	85.7	119.0	89.2	144	108	28	21	normal
	75	90	109.2	98.3	116.0	104.4	142	128	29	26	normal
	90	80	98.5	78.8	106.5	85.2	122	98	29	23	normal
	Totals	379		361		389		488		116	
E. J. S.	Res	40									
11-30-32	15	60	65.0	39.0	94.0	56.4	136	82	45	27	sm. amt. bile
	30	30	51.0	15.3	95.0	28.5	129	39	51	15	normal
	45	33	67.5	22.5	94.0	31.0	127	42	45	15	normal
	60	60	104.0	62.4	118.0	70.8	143	86	25	15	normal
	75	50	118.0	59.0	102.9	64.5	159	79	23	12	normal
	90	22	118.0	25.9	129.0	28.3	147	32	25	5	normal
	Totals	255		224		279		360		89	
12-7-32	Res.	130									
	15	13	74.5	9.6	86.7	11.2	134	17	54	7	normal
	30	15	70.2	10.5	80.5	12.0	113	17	56	8	normal
	45	54	74.5	40.2	84.5	45.6	134	72	52	28	normal
	60	46	112.0	51.6	118.0	54.2	152	70	24	11	normal
	75	68	110.0	74.8	118.0	80.2	154	105	24	17	normal
	90	38	103.0	39.1	111.0	42.1	143	54	29	11	normal
	Totals	234		226		245		335		82	
12-12-32	Res	42									
	15	26	40.0	10.4	57.0	14.8	140	36			sm. amt. bile
	30	20	39.0	7.8	55.0	11.0	127	25	77	15	normal; sl. red
	45	43	71.5	30.7	83.5	35.9	144	61	61	26	normal
	60	55	107.0	58.8	114.5	62.9					normal
	75	41	113.2	46.4	120.3	49.2	155	63	32	13	normal; sl. red
	90	19	96.0	18.2	108.0	20.6	144	27			
	Totals	204		172		194					
12-19-32	Res.	38									
	15	37	58.0	21.4	73.5	27.2	128	47	58	22	sm. amt. bile
	30	39	73.5	28.6	85.0	33.1	130	41	48	19	sm. amt. bile
	45	37	91.0	33.6	105.0	38.8	140	52	29	11	normal; sl. red
	60	48	105.5	50.6	113.5	54.5	148	71	23	11	normal
	75	33	102.5	36.5	118.0	38.9	144	47	25	8	normal; sl. red
	90	15	47.0	7.0	64.0	9.6	130	19	47	7	sm. amt. bile
	Totals	209		178		204		277		78	

*Analyses made before the beginning of $Al(OH)_3$ therapy.

TABLE II (Continued)

Gastric Analyses Following Histamine Injection in Patients Receiving $Al(OH)_3$ Therapy

Case Date	Specimen Min.	Vol. c.c.	Free Acidity c.c. 0.1 N Conc. per 100 c.c.	Free Acidity c.c. 0.1 N Total per Spec.	Total Acidity c.c. 0.1 N Conc. per 100 c.c.	Total Acidity c.c. 0.1 N Total per Spec.	Total Chloride m. Eq. Conc. per 1000 c.c.	Total Chloride m. Eq. Total per Spec. x 10	Total Base m. Eq. Conc. per 1000 c.c.	Total Base m. Eq. Total per Spec. x 10	Conditions of the sample
3. T. Mc.	Res.	15									
1-31-33*	15	18	68.5	12.3	88.6	15.9	123	22	43	8	normal
	30	20	79.0	15.8	95.0	19.0	133	27	39	8	normal
	45	42	100.0	42.0	112.0	47.0	145	62	31	13	normal; sl. br.
	60	41	102.0	41.8	116.5	47.7	143	59	36	15	normal; sl. br.
	75	40	102.0	40.8	116.0	46.4	144	57	28	11	normal; sl. rd.
	90	50	76.0	38.0	89.5	44.7	134	67	51	25	red tinge
	Totals	211		191		221		294		80	
2-10-33	Res.	20									
	15	10	34.4	3.4	56.0	5.6	104	10	63	6	blood +
	30	19	48.0	9.3	66.8	2.7	120	23	53	10	blood, trace
	45	20	80.0	16.0	92.5	18.5	138	28	49	10	normal
	60	53	100.7	53.3	113.0	59.9	142	75	35	19	normal
	75	48	104.5	50.1	117.4	56.3	143	69	30	15	normal; sl. br.
	90	46	103.5	47.6	116.0	53.3	144	66	31	14	normal
	Totals	196		180		206		271		74	
3-11-33	Res.	20									
	15	20	33.5	6.7	48.5	9.7	74	15	68	14	sm. amt. bile
	30	18	29.0	5.2	43.5	7.8	89	16	64	11	normal
	45	45	68.0	30.6	82.0	36.9	92	42	47	21	normal
	60	50	100.0	50.0	110.0	55.0	99	49	31	15	normal
	75	60	97.5	58.5	107.5	64.5	100	60	41	24	normal
	90	20	47.5	9.5	72.0	14.4	94	19	60	12	normal
	Totals	213		161		188		201		97	
4. A. E.	Res.	40									
2-17-33	15	19	28.0	5.3	45.0	8.5	102	19	60	11	normal; br. fl.
	30	25	19.0	4.7	36.0	9.0	89	22	59	15	normal; sl. rd.
	45	35	18.0	6.3	34.0	11.9	83	29	52	18	bile +
	60	28	43.0	12.0	66.5	18.6	106	30	48	13	normal
	75	33	25.0	8.2	40.0	13.2	88	29	54	18	normal
	90	20	16.5	3.3	36.0	7.2	89	18	52	10	normal
	Totals	160		40		68		147		85	
2-22-33	Res.	61									
	15	36	0.0	0.0	16.0	5.7	84	30	55	20	mucous ++; normal
	30	24	0.0	0.0	12.0	2.9	72	17	58	14	mucous ++; normal
	45	25	19.0	4.7	40.0	10.0	89	22	52	13	sl. amt. bile
	60	44	42.0	18.5	58.0	26.0	102	45	49	21	normal
	75	39	60.5	23.6	75.5	29.4	111	43	44	17	normal
	90	34	55.0	18.7	73.5	25.0	111	38	47	16	normal
	Totals	202		65		99		195		101	
3-1-33	Res.	60									
	15	20	12.0	2.4	29.0	5.8	90	18	66	13	bile ++
	30	20	12.0	2.4	28.5	5.7	80	16	61	12	mucous +; normal
	45	30	12.5	3.7	28.0	8.4	81	24	59	18	mucous +; normal
	60	25	34.0	8.5	50.0	12.5	98	24	48	12	normal; sl. rd.
	75	27	32.0	8.6	48.0	12.9	98	26	51	14	normal
	90	31	22.0	6.8	39.5	22.2	100	31	57	18	normal
	Totals	153		32		67		139		87	
3-4-33	Res.	30									
	15	18	38.0	6.8	55.0	9.9	96	17	57	10	mucous +; normal
	30	35	24.6	8.6	40.0	14.0	87	30	53	18	normal; sl. br. fl.
	45	29	25.5	7.4	42.0	12.2	86	25	57	17	normal; sl. br. fl.
	60	27	42.0	11.3	58.0	15.6	99	27	50	13	normal; sl. br. fl.
	75	18	45.5	8.2	63.0	11.4	101	18	55	10	normal; sl. br. fl.
	90	30	20.0	6.0	45.0	13.0	87	26	53	16	bile ++
	Totals	157		50		76		143		84	
5. G. Y.	Res.	35									
3-18-33*	15	30	35.0	10.5	51.0	15.3	119	36	71	21	normal
	30	55	87.0	47.8	103.0	56.6	133	73	42	23	normal
	45	70	93.0	65.1	105.5	73.8	136	95	33	23	normal
	60	75	113.0	84.6	123.5	92.7	152	114	30	24	normal
	75	70	109.0	76.3	121.5	85.0	150	105	30	21	normal
	90	55	77.5	42.6	97.5	53.6	139	76	45	25	normal
	Totals	356		327		377		499		137	
3-25-33	Res.	30									
	15	45	56.0	25.2	72.0	32.4	121	54	55	25	normal
	30	25	68.0	17.0	83.0	21.0	117	29	45	11	normal
	45	60	67.0	40.2	86.0	51.6	141	85	46	28	sl. red tinge
	60	85	88.5	75.2	102.5	87.1	143	121	49	42	sl. red tinge
	75	50	81.5	40.7	91.5	45.7	161	81	59	29	sl. red tinge
	90	32	86.0	27.5	100.0	32.0	134	43	40	13	sl. red tinge
	Totals	297		226		270		413		148	
4-15-33	Res.	22									
	15	15	35.5	5.3	48.3	7.2	106	16	72	11	normal
	30	20	56.0	11.2	73.0	14.6	111	22	63	13	normal
	45	50	86.0	43.0	98.0	46.0	120	60	44	22	normal
	60	56	114.5	64.0	122.5	68.6	121	73	31	17	normal
	75	65	90.0	59.5	110.0	71.5	125	81	32	21	bile ++
	90	55	74.0	40.7	86.0	47.3	114	63	37	20	bile ++
	Totals	261		224		255		315		104	
4-21-33	Res.	20									
	15	35	40.5	14.1	56.0	19.6	131	46	54	19	sm. amt. bile
	30	30	42.5	12.7	63.0	18.9	140	42	68	20	sm. amt. bile
	45	45	93.5	42.0	104.5	47.0	142	64	40	18	normal
	60	46	108.0	49.6	118.5	54.5	147	68	32	15	normal
	75	40	113.0	45.2	124.0	49.6	148	59	28	11	normal
	90	35	100.0	35.0	110.0	38.5	144	50	38	13	normal
	Totals	231		199		228		329		96	

*Analyses made before the beginning of $Al(OH)_3$ therapy.

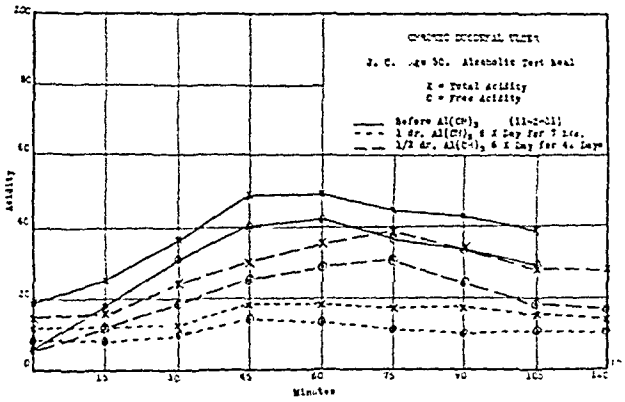


Fig. 3. Gastric acidity before and after receiving treatment as given above.

end of 60 minutes, being 30 minutes after the administration of histamine. Individual treatment is recorded in the protocols for each patient.

CASE PROTOCOLS

Case I. Hospital No. 109863. H. V., male, aged 35, truck driver, weight 140 lbs. Present illness was "pain in the abdomen." History revealed an operation for ulcer several years previous and on the strength of clinical and X-ray findings a diagnosis of duodenal ulcer was made. Patient was admitted to the hospital on Nov. 25th and placed upon a 4th day Sippy diet. Gastric analyses were made on Nov. 28th and 30th, before any aluminum hydroxide cream was given. On Dec. 1st medication consisting of 15 c.c. of $Al(OH)_3$ cream in 1 ounce of milk six times per day was begun. No other medication was given except an occasional prescription of 1 ounce of petrolagar twice a day. Gastric analysis was made on Dec. 5th and 7th after which patient was permitted to be up and around the Ward. Analysis was again made on Dec. 12. Patient was discharged on Dec. 14 and given aluminum hydroxide cream with instructions to take 4 cc. six times per day. The symptoms of which the patient complained upon entry were relieved as soon as the $Al(OH)_3$ therapy was instituted and at the time of discharge his condition and prognosis were very good. Gastric analysis was again performed on Jan. 18 when the patient visited the Out-Patient Clinic.

Case II. Hospital No. 109867. J. S., male, aged 55, white, laborer, weight 145 lbs. Present illness was complaint of epigastric pain. A diagnosis of duodenal ulcer was made on the strength of clinical and X-ray findings. There were no indications of retention but severe constipation was habitual. Patient was admitted to the hospital on Nov. 26th with severe pain in the epigastric region. Aluminum hydroxide cream, 8 c.c. six times per day, and the 4th day Sippy diet were immediately given. No other medication was given except an occasional sedative (luminal) on the evening of the day the gastric analysis was performed, and frequent enemas and suppositories. Relief of gastric symptoms was obtained immediately after the use of the cream. Gastric analyses were performed on Nov. 30th and Dec. 7th, 12th, and 16th. Patient was discharged Dec. 28th, clinically improved, and was given $Al(OH)_3$ cream with instructions to use it in dosages of 4 c.c. six times per day.

Case III. Hospital No. 112346. T. Mc., male, aged 54, white, salesman, weight 179 lbs. Present illness was attacks of substernal pain. Fluoroscopic examination and roentgenograms of the stomach showed an inconstant deformity of the duodenal bulb, which was persistent in the prone position, but no niche could be seen. No retention was found at 6 hrs. The changes were diagnosed as due to a duodenal ulcer and therapy for such was indicated by other clinical findings. Patient was admitted to the hospital on Jan. 27th and placed upon a first day Sippy diet until Jan. 30th when the convalescing Sippy diet was ordered. Gastric analysis was performed on Jan. 31st, and on Feb. 1st the first medication of aluminum hydroxide cream was given in doses of 8 c.c. six times per day. Gastric analysis was again made on March 11th. During the interval between hospitalization and this analysis, the patient had had no gastric symptoms and felt much improved.

Case IV. Hospital No. 112601. A. E., male, aged 46, white, unemployed, weight 155 lbs. Present illness was "pain in the stomach." Fluoroscopic study and roentgenograms revealed a large benign ulcer of the lesser curvature of the stomach measuring about 3½ c.c. in diameter. Thirty per cent retention at 6 hours was found and a niche indicating a duodenal ulcer was also present. Second examination, 25 days later, showed the niche to be smaller. Patient was admitted to the hospital on Feb. 1st and placed upon a liquid diet. On Feb. 4th the convalescent Sippy diet was ordered. Gastric analyses using 50 c.c. of 7 per cent alcohol as a stimulant were performed on Feb. 7th and 10th. Four c.c. of $Al(OH)_3$ cream six times per day was ordered beginning on Feb. 9th and histamine analyses were made on Feb. 17th and 22nd and on March 1st and 4th. Through error the patient was permitted to take 8 ounces of magnesium citrate water on Feb. 15th. The improvement in the patient was such that he was released to the Out-Patient department on March 7th with instruction to continue on 4 c.c. of the cream daily and to report weekly.

Case V. Hospital No. 53955. G. V., male, aged 47, white, plasterer, weight 128 lbs. Present illness was described as "stomach trouble" with epigastric burning 2 to 3 hours after meals. Fluoroscopic examinations and pictures of the stomach showed thickening of the rugae of the stomach and peristaltic waves having a spastic character at times. On both examinations the stomach was very active and showed an area of constriction about 1 cm. beyond the pyloric canal. This constriction varied in width indicating that, besides an organic deformity, a spastic condition was also present. A niche measuring about 8 mm. in diameter could be seen about the mid-portion of the bulb a little nearer to the greater curvature side. At 6 hours no retention was found. The diagnosis was duodenal ulcer with possibly another at the pyloric canal. This patient was followed in the Out-Patient department and reported severe pains which awakened him at 3:00 to 4:00 A. M. Food was found to relieve the pain somewhat. No vomiting or nausea was present but the bowels were very constipated. No blood was passed in the stools. Mild tenderness could be elicited in the epigastric region. Gastric analysis was made on March 18th and the patient was placed upon 4 c.c. of $Al(OH)_3$ cream six times per day immediately thereafter. Subsequent analyses were made on March 25th and April 15th and 21st. After beginning the cream no distress was reported at any time except that a headache usually occurred after an analysis. Patient last reported to the Clinic on May 19th. No distress occurred since therapy was instituted.

DISCUSSION

During the past several years one of us (E.) has treated over 125 peptic ulcer patients with colloidal aluminum hydroxide and obtained uniform clinical results. Within a few days after beginning the cream all burning, nausea, and pain disappear. Feedings are taken without distress and weight gradually increases. There have been no idiosyncrasies to the drug, no vomiting, no toxic symptoms or complaints or evidence of gastric intolerance.

The typical cases which have been studied intensively do not disclose the ultimate mechanism of the beneficial results in the use of aluminum hydroxide

cream. However, some very important and interesting results of its use are apparent.

Gastric Analyses. The volume of gastric secretion for a 90 minute period shows a tendency to decrease after the administration of colloidal $Al(OH)_3$. In the course of a single analysis the volume shows, in many cases, a small decrease for the second 15 minute period.

TABLE III

Acid-Base Findings of Blood. First specimen taken before test meal, second specimen sixty minutes after meal

Case	Date 1932-33	Chlorides m. equiv.	Total Base m. equiv.	CO_2 Content vol. per cent
1. E. V.	Nov. 28	99	149	57.0
		99	154	58.0
	Nov. 30	98	149	59.7
		99	153	66.5
	Dec. 5	94	149	53.0
		97	146	54.8
	Dec. 7	102	148	57.0
		101	146	61.4
	Dec. 12	100	148	56.0
		99	147	59.8
	Jan. 18	104	153	62.6
		103	157	61.1
2. J. S.	Nov. 30	100	152	69.0
		100	156	68.9
	Dec. 7	98	148	57.9
		98	150	59.2
	Dec. 12	100	147	64.5
		102	152	61.1
	Dec. 16	88	149	59.8
		87	151	64.9
3. T. Mc.	Jan. 31	97	151	63.6
		96	150	61.7
	Feb. 10	97	145	57.9
		96	146	61.7
	Mar. 11	98	145	60.4
		99	143	54.1
4. A. E.	Feb. 17	98	143	52.1
		96	144	55.1
	Feb. 22	98	144	54.0
		99	143	53.2
	Mar. 1	97	144	54.1
		98	143	57.3
	Mar. 4	98	143	54.1
		99	145	54.8
5. G. Y.	Mar. 18	98	148	59.8
		97	150	63.6
	Mar. 25	97	146	52.2
		99	142	57.9
	Apr. 15	98	148	55.0
		100	146	56.0
	Apr. 21	100	148	48.5
		100	147	48.0

This has been attributed by Bloomfield and Keefer (16) to the subsidence of stimulation arising from the passage of the Rehfuss tube.

The concentration of free acid in the first and second 15 minute specimen shows a decrease, in most analyses, as the duration of $Al(OH)_3$ therapy increases (see Table II). This is a very significant finding inasmuch as reduction in gastric acidity is one of the primary objects in treating ulcer. The decrease begins to show immediately after the initiation of the treatment and shows a progression to a lower level. Thus less irritation to the ulcer is present, and the amount of alkali required for the neutralization of the stomach contents as they pour into the duodenum is decreased. The efficacy of the colloidal aluminum hydroxide must then rest, at least partially, in the reduction of the concentration of free acid. Its slight astringency and demulcent properties are doubtless also important therapeutic properties.

It is natural that since aluminum hydroxide cream is used as a colloidal protein precipitant, its effect on the stomach mucosa should be questioned. One of the most important findings with regard to the free acid concentration is the fact that histamine can elicit approximately the same concentration at the height of stimulation, before and after the use of aluminum hydroxide cream. This is an indication that the cream does not impair the ability of the stomach to secrete acid.

In cases showing high acid values the free acid curves and the total acid curves are closely parallel. It follows that the highest total acid concentration occurs in those specimens which show the highest free acid concentration. Especially is this true in analyses using histamine as a stimulant. The analyses reported here agree with the findings of many other workers to the effect that as the secretion volume increases under histamine stimulation, the free acid concentration rises and the character of the gastric secretion becomes less mucoid. The highest acid concentration was usually reached in the second 15 minute period after the injection of histamine, but occasionally it was not attained until the next 15 minute specimen. Varying rates of absorption of the histamine could very easily account for this. It may be noted that the greatest amount of free acid is not always secreted in those periods showing the highest acid concentration.

Berglund, Wahlquist and Sherwood (17) demonstrated that the total chloride was a true index of the acid secretion of the stomach stimulated by histamine. They believed that only insignificant amounts of chloride existed in the gastric juice in a form other than as HCl. The difference between free and total acidity was considered as due to combination of HCl with mucus. Considering the total acidity of these cases it is found that the individual specimens show a high degree of correlation; thus supporting the above workers.

Polland, Roberts and Bloomfield (18) studied the chloride, base and nitrogen content of the gastric juice after histamine stimulation. They found that the rise of chloride concentration was paralleled by an increase in volume but the latter was observed to fall more quickly than the former. In these cases, however, it is noted that the total chloride concentration and the volumes are parallel throughout the rise and fall of secretion.

Further evidence that no permanent injury is done to the secreting cells of the stomach is contained in those cases where values for total chloride secreted in 90 minutes rose again when the dosage of aluminum hydroxide cream had been reduced to one-fourth its former value.

The total base shows no close correlation with the volume of secretion in these cases (Table II), but the total base values are closely correlated by an inverse relationship to the figures for free and total acid concentration. Bulger, Stroud and Heideman (19) studied the electrolyte variation in human gastric juice obtained by water stimulation and found that relatively little change in the concentration of chloride attends secretion but that the total base falls in proportion to the increase in acid under their experimental conditions. Austin and Gamon (20) found that the period of maximal sodium secretion after histamine is previous to the period of maximal acid secretion and not when the acid secretion is subsiding. The potassium content remained approximately constant while the

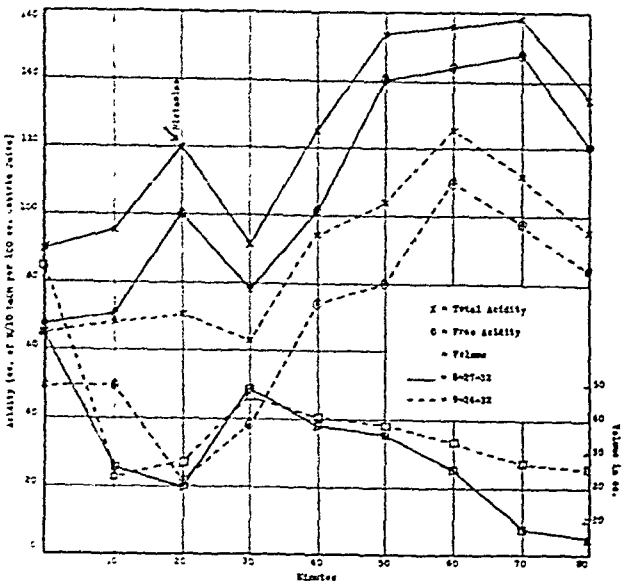


Fig. 4. Bloomfield gastric analysis on chronic duodenal ulcer case before and after treatment with a Colloidal $Al(OH)_3$.

amounts of calcium and magnesium were so small that their variation was not easily determined. Polland, Roberts and Bloomfield (18) found a general decrease in base concentration as the volume of secretion increased, and noted also that the base and volume fell together for a period, indicating that dilution was not alone the factor responsible for the decrease in base concentration. However, in the present study the correlation of total base and the volume of secretion is very poor, although the general tendency is for the least concentration of base to occur when the volume is greatest.

Blood Findings. The disturbance of the acid-base equilibrium of the body which accompanies the ingestion of large quantities of soluble alkali has been reviewed by Gatewood, Gaebler, Muntwyler and Myers (21). Wildman (22) made a valuable contribution to the subject of chloride metabolism and alkalosis in peptic ulcer cases receiving bicarbonate therapy. He found that there must be a marked reduction of chloride reserve in the body before gastric secretion is definitely affected, and that acid secretion cannot be controlled by restriction of chloride intake. When gastric secretion is lowered by hypochloremia the ratio of chloride in the corpuscles to the chlorides in the plasma $\frac{(Cl_c)}{(Cl_p)}$ is reduced. Similarly the ratio of chlorides in the tissue cells to the chlorides in the tissue fluids $\frac{(Cl_c)}{(Cl_f)}$ is reduced. He suggests that the lowering of this ratio in reference to the sensitive nerve cells may be the basis of the apparent dysfunction of the autonomic system as seen in the symptoms of alkalosis.

The search for a suitable insoluble antacid finally led to the trial of aluminum hydroxide preparations because they are not absorbed and have antacid properties. Myers and Killian (23) determined that approximately 25 per cent of the aluminum from ingested baking powder residues supposedly in the form of $Al(OH)_3$ was in solution in the stomach and duodenum when straight sodium aluminum sulfate baking powders were used. However, the investigations of Myers and Mull (24), Myers and Morrison (25), Wührer (26) and others prove that there is practically no absorption of aluminum from the intestinal tract. No apparent disturbance in the mineral metabolism of the body by the ingestion of even large quantities of aluminum is found.

It was found by Dodds and Smith (27) that during the first 40 minutes after a meal the whole blood, plasma, and corpuscle chloride content showed a fall which they attributed to the beginning of gastric secretion. During the period between 45 and 90 minutes the whole blood showed a recovery to normal with an increase in corpuscle content above normal. The plasma chloride remained low. Gram (28) studying the serum chloride in various diseases found that an increase or decrease is accompanied by a corresponding percentage change in whole blood chloride. Arnoldi (29) had observed that the chloride of serum is altered during digestive activity and that in hyperacidity the amount was less than in hypoacidity. Molnar and Hetenyi (30) on the contrary, found that the serum chloride remained within the normal limits, although towards the lower bracket in anacidity and toward the upper in hyperacidity. Lim and Ni (31) reported that the fall in blood chlorides during histamine stimulation was greater in the corpuscles than in the plasma. A lowering of plasma chloride averaging 23 mg. was found by Jordan (32) in patients receiving soluble alkali therapy for ulcer. Bloch and Serby (33) found that the blood chloride picture did not differ from normal in 20 ulcer cases which they studied.

The data obtained in this study show, however, that no hypochloremia existed even after the aluminum cream had been ingested for several months. The normal range of plasma chlorides in terms of milli-equivalents is from 99 to 108 per liter. Assuming that the normal serum chloride level is about the same as that of the plasma, we find that most of the serum chloride figures observed in this investigation, both before and after the cream was given, fall in the lower limits of the normal range. However, no variation is found in a given individual during the height of stimulation of gastric secretion by histamine.

The total base findings, both before and after histamine stimulation, show no change in concentration within the limits of experimental error. The determinations were made in duplicate and all values obtained, both before and after the use of the aluminum cream, fall within the normal range for serum, but have a definite tendency toward the lower limit. The values range from 142 to 157 milli-equivalents per liter.

Berglund, Wahlquist and Sherwood (17) found that a close correlation existed between the highest total chloride concentration in a gastric analysis and the blood base concentration. Sunderman (34) did not find this in patients with pneumonia. In our data the correlation exists in most cases.

The alkaline reserve of the plasma (CO_2 capacity) is an adequate index of the acid-base balance only as long as variations from the normal are compensated. Therefore, the determination of the blood pH is highly desirable in the study of the acid-base balance. Since it was impractical to make such determinations under the conditions of this investigation, the chloride, total base, and carbon dioxide content had to be relied upon for information concerning the acid-base equilibrium.

However, acid-base determinations, including pH, were made on a single case receiving 108 c.c. of alumina cream daily for one week, the data being reported elsewhere (6). The variations in the pH (0.03) were within the limits of error of the method. Myers and Booher (35) studied the blood of patients with peptic ulcer receiving alkali treatment and found "that the bicarbonate invariably rises before the pH becomes abnormal." Jordan (37) studied the acid-base equilibrium in similar cases and found that toxic symptoms of alkalosis did not occur until the carbon dioxide content had risen above 70 volumes per cent. On this evidence it seemed that a study of carbon dioxide content would be profitable as an indication of acid-base balance variations in this study.

The highest figure for carbon dioxide content in any instance in these cases is 69 volumes per cent. This occurred in Case II before any aluminum cream had been administered. One week later it had fallen to 59 volumes per cent. In most instances the carbon dioxide content did not rise above 60 volumes per cent, and at no time did any subject show a value exceeding 70 volumes per cent. The highest content found while a patient was receiving aluminum hydroxide cream was not above 65 volumes per cent.

Histamine injection in the amount used in these cases does not cause any marked change in the carbon dioxide content (36, 37). The highest difference between the level before and after the injection was 6.8 as seen in Case I. Other factors such as increased ventilation, etc., may be instrumental in creating this difference, although care was exercised to minimize these factors. It is believed, however, that these additional factors are largely instrumental in producing the difference between the levels of CO_2 before and after the injection, rather than the injection itself, inasmuch as the difference is less than the experimental error in many cases.

The blood data in Table III show that no significant deviation from the initial level occurs in the chlorides, total bases, or carbon dioxide content of the serum after the use of colloidal aluminum hydroxide as an antacid, nor do they significantly change at the height of gastric secretion under histamine stimulation in these cases. A possible compensatory mechanism which would temporarily balance the secretion of large amounts of hydrochloric acid in the stomach is seen in the findings of Neale and Klumpp (38) who observed an increase in the alkalinity of the pancreatic secretion during histamine stimulation of the gastric secretion.

SUMMARY

The present observations on the effect of colloidal aluminum hydroxide upon the gastric secretion and upon the blood serum chlorides, total base and carbon dioxide content lead to the following conclusions:

1. With respect to the secretion of gastric juice after the ingestion of colloidal aluminum hydroxide:

The highest acid concentration of the gastric secretion after the intramuscular injection of histamine usually occurs between 15 and 30 minutes after the injection and occasionally during the following 15 minute period, showing that no change from normal occurs.

The greatest amount of acid is not always secreted in the 15 minute period yielding the highest acid concentration.

The total chloride concentration is an adequate index of the acid concentration, as is normally the case.

The total chloride concentration and the volume of secretion usually show a parallel rise and fall.

The total base concentration of the gastric juice is closely correlated to the free and total acid concentrations and hence to the total chloride concentration.

Only a general correlation exists between the volume of secretion and the total base concentration or the total amount of base per specimen.

2. With respect to the use of aluminum hydroxide as a gastric antacid:

A decrease in the total amount of acid secreted occurs in 90 minutes, this decrease being especially marked in cases of hyperacidity.

A decrease in free acidity of the gastric juice is shown by lower figures for free acid concentration in the two specimens collected at each analysis before the injection of histamine.

While the decreases mentioned are manifest immediately after administration of the colloidal aluminum hydroxide, a progression toward a lower level of acidity is seen with the duration of its use.

It would not appear that these decreases in acidity are the result of any permanent damage to the secreting mechanism, since histamine continues to elicit the same high acid concentration even after this antacid has been administered for several months, and further since a reduction in the dosage results in a rise towards the pre-treatment level.

Judging from a review of the literature on gastric antacids, from the observations on the relief of the symptoms of peptic ulcer in this study, and from the laboratory findings here reported, it appears that colloidal aluminum hydroxide is the most satisfactory antacid thus far employed.

3. With respect to the acid-base equilibrium of the blood of patients receiving aluminum hydroxide for a period of several months:

No significant change occurs in the serum chloride, total base or carbon dioxide content but the small changes exhibited show a tendency for the total chlorides to rise, and the carbon dioxide to fall—away from alkalosis.

No significant change occurs in the serum chloride, total base or carbon dioxide content one-half hour after the intramuscular injection of 0.1 mg. of histamine per 10 kilo of body weight.

The use of colloidal aluminum hydroxide over a period of several months is attended by no disturbance in the acid-base balance of the blood.

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SECTION VI—*Abdominal Surgery*

Diverticula of the Jejunum: Report of Four Cases*

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RANKIN *and Martin in reviewing* 111 *cases of* diverticula of the duodenum and three cases of diverticula of the jejunum in which the diagnosis was made by roentgen examination of the gastro-intestinal tract, concluded that (1) diverticula of the duodenum are of less clinical importance than diverticula elsewhere in the small bowel (2), no typical symptoms can be ascribed to diverticulosis of the small bowel, and (3) careful medical management seems to be the best procedure in the majority of the cases, although occasionally surgical intervention seems warranted.

Reviews of the literature on diverticulosis of the jejunum have been made by Gisbertz (2), and by Helvestun (3), and cases have recently been reported by Beigler, Bloom and Wruble (4), and by Schmidt and Guttman (5). All authors agree that no specific syndrome is associated with diverticulosis of the small bowel, that clinical diagnosis is usually impossible, and that careful medical management is the treatment of choice. Occasionally, however, the symptoms resulting from diverticula of the small bowel are so intractable that surgical intervention is necessary as is illustrated by the following case.

CASE REPORTS

Case 1: The patient was an unemployed painter, 32 years of age who entered this Clinic complaining of a gnawing epigastric pain which came on 45 minutes after meals. The pain was relieved by food, but was not relieved by soda. These attacks which had been present for 2 years preceding our examination were accompanied by

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some eructations and were aggravated by fatty foods, cabbage, and onions. At the onset of the gastro-intestinal disturbance, the patient had had an attack of agonizing colicky pain which began in the region of the umbilicus and radiated into the right lower quadrant. This pain was accompanied by nausea and vomiting and was so severe as to require morphine for relief. Two days before entry, the patient had had a similar attack of pain which had lasted for 12 hours. There was no history of jaundice, fever, or clay-colored stools.

For the past three years, the patient had had severel frontal headaches which lasted from 12 to 24 hours and were accompanied by nausea and vomiting. Ordinary dietary and medical management had given him no relief.

Physical examination revealed no abnormal findings. The heart and lungs were normal, the abdomen was flat and soft, and there were no masses palpable, no enlargement of the liver or spleen, and no tenderness was present.

Laboratory studies showed that the urine was entirely normal. The red blood cells numbered 4,790,000; white blood cells, 5,800; and the hemoglobin was 97 per cent. The blood sugar was 116 mg. per 100 c.c. five hours after eating and the Wassermann and Kahn tests were negative. An Ewald test meal was given and the free acid was found to be 38 and the total acid was 51 per cent. A cholecystogram was reported to show a normally functioning gall bladder without stones. The stomach and duodenum were reported to be normal except for a diverticulum 3 cm. in diameter which was attached to the first portion of the duodenum. This remained filled for 24 hours. The colon was normal.

Because of the severity of the patient's symptoms and the failure of medical management, excision of the diverticulum was advised.

Operation: (Dr. Jones). On October 16, 1935, an upper right rectus incision was made under spinal anesthesia and the gall bladder and liver were explored and found to be entirely normal. A normal appearing appendix was removed and its stump was inverted. The transverse colon was then pushed upward, an incision was made in the parietal peritoneum and the duodenum was exposed. The entire duodenum was carefully explored but no trace of a diverticulum or any other abnormality could be found. Finally, however, a pouch was seen over toward the midline; this pouch was grasped, dissected out and found to originate from the posterior wall of the jejunum at a point 2 cm. below the ligament of Treitz. The sac was dissected free down to a base about 2.5 cm. in diameter which was grasped with a Kelly clamp. The pouch was then excised and its base closed over by two lines of continuous inverting sutures. The abdomen was closed in layers in the usual manner.

Pathology report: Pathologic examination of the excised diverticulum showed that it was 4 cm. in length, 2.5 cm. in diameter at the orifice and 1.3 cm, in diameter at the distal end. The walls of the diverticulum varied from 1.0 to 2.0 mm. in thickness and were composed of normal jejunal mucosa covered by a thin fibrous coat. There was no active inflammation or ulceration.

The appendix showed a patent lumen, a moderate amount of lymphoid tissue, but no evidence of acute or subacute inflammation.

The postoperative course was uneventful, the maximum temperature being 100.4° F. and the pulse never rising above 100. The patient was discharged on the fifteenth postoperative day at which time he was able to take a full soft diet and he experienced no dyspepsia or abdominal pain.

A letter from the patient six weeks after the operation stated that he was eating a full diet, had had no recurrence of the gastro-intestinal symptoms, and that the headaches had been much less frequent and severe and that he felt entirely well.

Only three other cases of diverticulum of the jejunum have been seen at the Cleveland Clinic. In each case, the diagnosis was made from information gained from the roentgen examination.

Case 2: The patient was a woman 67 years of age. Roentgen examination of the stomach showed an ulcer in the pars media on the lesser curvature, two large diverticula from the second portion of the duodenum, and multiple diverticula from various parts of the small intestine. The only symptoms were indefinite abdominal distress which occurred chiefly in the left upper quadrant two hours after meals. It is, of course, impossible to state whether the symptoms in this case were due to the ulcer or to the diverticulosis. In view of the patient's age and the multiplicity of the lesions, medical treatment was advised.

Case 3: The patient was a man 42 years of age who was admitted complaining of a sour stomach, belching, and a sensation of epigastric fulness and soreness. All symptoms were of 10 years' duration but there had been frequent remissions of several months duration. The distress came on 10 or 15 minutes after meals and lasted four or five hours. Food or soda gave temporary relief. The patient had lost 30 pounds in weight. There had been no vomiting and no colicky pain or jaundice.

Physical examination: Physical examination revealed no abnormality except slight epigastric tenderness. Roentgen examination of the gastro-intestinal tract showed a non-obstructing duodenal ulcer, a normally functioning gall bladder without stones, and a normal colon. In addition, one film showed a probable diverticulum of the jejunum. There were 69 units of free hydrochloric acid and 88 units of total acidity after an Ewald meal. Blood counts, urinanalysis and all other routine laboratory studies gave findings within normal limits.

Diagnoses of duodenal ulcer and diverticulum of the jejunum were made, and the patient was given a modified Sippy diet with milk and cream and calcium carbonate powders between meals.

Six weeks later, a letter from the patient's wife stated that his stomach troubled him much less, although he still occasionally experienced a sensation of epigastric soreness.

Again in this case, it is probable that the symptoms were the result of the ulcer and not of the diverticulum.

Case 4: The patient was a married woman 40 years of age who came to this Clinic in December, 1925, complaining of severe frontal headaches, loss of appetite, vomiting after meals, and of a constant, severe, burning, epigastric pain which was aggravated by food. She had lost much weight and red blood had appeared in the stools on three or four occasions. All symptoms were dated to the time of a fall three months prior to entry.

Physical examination revealed no abnormal findings except for marked epigastric tenderness and tenderness at McBurney's point.

Laboratory findings: Routine studies of the blood and urine revealed no abnormalities. Roentgen examination of the gastro-intestinal tract showed a diverticulum of the second part of the duodenum, a second diverticulum at the duodenojejunal junction, and one farther along in the small intestine.

At operation, Dr. George Crile, Sr., found a large number of diverticula in the mesenteric border of the small bowel. The larger ones were dissected free, ligated and their stumps inverted by means of purse-string sutures. The postoperative course was uneventful except for a slight wound infection. On the eighteenth day after operation, the patient was discharged from the hospital.

Six months later, she stated that her general condition had improved strikingly, and that she was having no abdominal pain and only occasional headaches.

DISCUSSION

In cases 1 and 4, the patient's symptoms were, in all probability, the result of the diverticula but in the other two cases, it is unlikely that the diverticula represented more than an incidental finding. Certainly, the active peptic ulcers present in cases 2 and 3 were sufficient to explain all symptoms.

The association of severe headaches with the abdominal distress in the two cases in which the abdominal symptoms were definitely caused by the diverticula is interesting, although the series is of course too small to make these observations of any value. Diminution of intensity and frequency of the headaches occurred in both cases after the removal of the diverticula.

Unfortunately, there is nothing specific in the histories of patients with diverticula of the small bowel that can aid in making the clinical diagnosis. If however, a patient has gastro-intestinal symptoms consisting of pain and eructations following meals, if there is no roentgen evidence of peptic ulcer or of biliary disease, and if disorders of the colon can be excluded, it is well to bear in mind the possibility of a diverticulum of the small bowel and refer the patient to the roentgenologist with a request that especial attention be given to this question so that appropriate examinations can be made.

Medical management, emphasizing a bland diet and barium sulphate or olive oil given before meals, is often sufficient to control the symptoms referable to diverticula of the small bowel, but when the diverticula are in the jejunum, the symptoms are not infrequently quite intractable and surgical intervention becomes necessary.

SUMMARY

1. Four cases of diverticula of the jejunum are reported.

2. In one case, roentgen examination showed that the diverticulum appeared to arise from the first part of the duodenum, but at operation, it was found to come from the jejunum just below the duodenojejunal junction.

3. The two patients who did not respond to medical management were completely relieved of symptoms by excision of the diverticula.

4. There is no characteristic syndrome which makes possible a clinical diagnosis of diverticulum of the small bowel.

5. Persistent pain and eructation after meals in the absence of peptic ulcer, biliary disease, or disorders of the colon should suggest the possibility of a diverticulum of the small bowel, particularly if the symptoms are accompanied by severe headaches.

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SECTION VII—*Surgery of the Lower Colon and Rectum*

Ischio-Rectal Abscess: A Stage in the Development of "Horseshoe" Fistula*

A Case Report

By

GEORGE M. LANDROCK, M.D.†
PHILADELPHIA, PENNSYLVANIA

THE patient, a male, twenty-eight years old, came to the dispensary on November 9th, 1935.

He gave a history of sudden onset of malaise, fever and inability to sleep for two nights on account of throbbing pain and swelling to the right of the anus.

Examination revealed a circumscribed swelling involving the right ischio-rectal fossa. The overlying skin was reddened, felt hot and indurated, and was tender upon pressure. There was, in the central portion, a small area the size of a quarter, which was paler in color and fluctuation was noted upon careful palpation. At examination the pain was so severe that neither digital nor instrumental examination was deemed necessary.

An *emergency diagnosis* of acute ischio-rectal abscess seemed logical.

Operation: Under local anesthesia, a paramedian incision was made into the abscess cavity. About four ounces of foul-smelling pus were evacuated, the fluid being under considerable tension. The patient was told to take hot sitz baths twice daily and to apply hot moist boric acid dressings locally, and was admitted to the hospital on the following day for further operative procedure.

The patient stated he had suffered from piles, (his own diagnosis) for many years and had sought relief by self medication with various ointments and suppositories.

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Submitted February 28, 1936.

Upon admission at the hospital his temperature was 99.6° F. and pulse rate 70. The blood pressure and urinary findings were within normal limits. Discharge from the incised abscess was scant and there was slight redness and induration of the overlying skin.

Under gas-ether anesthesia, the previous incision was enlarged. All septa were broken down for better drainage. The infection involved the anterior and posterior portions of the right ischio-rectal fossa. There was a communication posteriorly with the fossa on the opposite side, forming a posterior "horseshoe" abscess and fistula.

At operation, the internal opening was found in a posterior crypt. The fistulous tract extended downward, dividing into two branches, just proximal to the external sphincter, one communicating with the abscess through a short tract between the internal and external sphincters, and the other continuing superficially under the anal skin, ending at the posterior commissure. A hook was inserted into the crypt and this superficial tract *excised*, leaving the external sphincter intact. The deep tract was not divided at this time. A stab wound was made over the posterior portion of the left ischio-rectal fossa and a rubber tube inserted to afford through and through drainage. The cavity was packed lightly with gauze.

Post-operative treatment consisted of hot moist boric acid compresses changed frequently. The gauze dressing was removed on the day after operation. The rubber drain was removed on the third day. The wound was treated daily with a mild antiseptic until the patient's dismissal from the hospital on the eighth day. Thereafter he was seen twice a week, the cavity healing by granulation in about seven weeks, except for a small short sinus at the posterior angle of the wound. He was last seen on January 10th, 1936, at which time the sinus was still present. If this sinus does not heal, further division may be necessary.

Perianal Lipoma: A Case Report*

By

MAX I. LOMAS, M.D.†

PHILADELPHIA, PENNSYLVANIA

THE patient, a Negro, male, aged 51 years, registered at the Clinic October 19th, 1935, complaining of a "lump" near the anus on the left side. An operation for a "swelling" at the same site had been performed at another hospital eight years previously.

Six months before admission the patient noticed the present swelling. Local soreness was present occasionally. No discharge had been noticed.

Family history and past personal history were unimportant except as noted.

Examination revealed a swelling three inches long and two inches wide, one and one-half inches to the left of the anus. The swelling was moderately firm, showing no definite fluctuation. No local heat nor tenderness could be detected. Examination of the anus, rectum and sigmoid revealed no abnormalities. Inspection of the rest of the body showed no swellings or tumors of the same type.

A tentative diagnosis was made of a perianal lipoma or a 'cold" abscess. The swelling was incised under gas-ether anesthesia. The tumor was found to consist of fatty tissue. This was enucleated down to the ischio-rectal fossa where it apparently was continuous with the fat of this fossa. A ligature was placed around the base of the tumor and the tumor was excised. The wound was closed by interrupted sutures and healed by primary union.

Although fatty tumors of lipomata of the buttock frequently are reported, perianal lipomata continuous with or contiguous to the normal fat contained in the ischio-rectal fossa are not commonly encountered.

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Submitted February 28, 1936.

Annual Abstracts of Protologic Literature

(May, 1934-May, 1935) By CLEMENT L. MARTIN, M.D., Chicago, Illinois

The complete bibliography from which these Abstracts were made will be published in full in the Transactions of the American Proctologic Society, 1935.

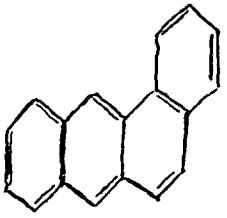
ANESTHESIA

Spinal anesthesia is finding its place; it has gained wide usage as the details of its administration have become better known. A number of surgeons have completely abandoned it after liberal trial, some anaesthetists still use it fearfully but surgeon and anaesthetist have another valuable addition to their armamentarium in properly used spinal block analgesia. Trans-sacral and caudal block analgesia has the commendation of some; it is more difficult to give and takes longer than a spinal but if only the 2nd sacral foramina are injected in addition to the caudal canal, as is the case usually for rectal operations, the injections are not very difficult. It is very safe as the anaesthetic solution remains extra-dural; it affords a well-relaxed, well-anaesthetized field.

Avertin as a basal or preliminary anaesthetic continues to receive some condemnation but more favorable reports. Evipal given intravenously appears to be especially indicated where a short anaesthetic, of 15 to 20 minutes duration suffices. Newer drugs have been tried in infiltration anaesthesia. The use of diothane in 100 anal cases is reported by *Rosser*. He found it gave anaesthesia enduring "several, to 24 hours," the results were not uniform, a tendency to skin tag formation following its use is noted. A few cases had abscess but the use of normal saline solution to replace the distilled water in which the diothane was dissolved, avoided this complication. 1 ounce of either the 1% or 0.5% solution was used.

Bacon used nupercaine in 91 anal operations and summarizes his results thus: it may be used without ill effects,

its initial effect is somewhat slower than procaine but the duration is prolonged by a few hours; in amounts not exceeding 70 c.c. of a 1:1000 solution it may be injected safely and efficiently. Various ointments containing nupercaine, pantocaine and other synthetics, having a more enduring action than procaine or benzocaine have been placed on the market.



No. 1. 1:2—Benzanthracene

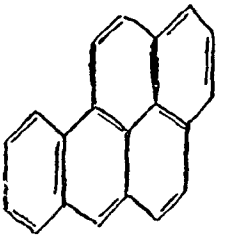
Frankfeldt in Yeoman's Clinic states he has used nupercaine in Gabriel's formula in 150 cases in a 2 year period and found it valuable. The solution is made up of 0.5% nupercaine base, 10% benzylalcohol, 1% phenol in rectified almond oil. It is not used in the ordinary hemorrhoidectomy but has its field in external thrombotic hemorrhoids, pruritus ani, fissure, short fistulae, and anal neuroses.

CANCER

Progress: In the last two years a correlation has been made of some previous and much recent data in the field of cancer research. It has been determined that there is a close relationship both chemically and in biologic effect between some of the hydrocarbons in tar and estrogenic hormones. The tricyclic phenanthrene ring system is common to a group of carcinogenic hydrocarbons. Compounds related to 1:2 benzanthracene, which is itself inactive, have been made to produce carcinoma. The principal carcinogenic hydrocarbons thus far found are (1) 1:2 benzpyrene, one of the most active substances; (2) 5:6 cyclopenteno-1:2 benzanthracene; (3) 1:2:5:6 dibenzanthracene; (4) 9:10 dihydroxy-9:10 di-n-propyl-9:10 dihydro-1:2:5:6 dibenzanthracene; (5) 6 isopropyl-1:2-benzanthracene; (6) various other derivatives of 1:2:5:6 dibenzanthracene; (7) chrysene. All of these substances have produced either carcinoma or sarcoma, rats and mice being used principally. These agents do not produce cancer directly as the agent of Rous sarcoma does, but indirectly. Carcinogenic substances similar to those mentioned might conceivably arise from sterols normally present in the body, it has been suggested by *Kennaway* and *Cook*.

"The hydrogenated phenanthrene ring type of compound, as already pointed out, only recently has been recognized as a normal constituent of the body. Mainly through the work of *E. L. Kennaway* and his co-workers at the Cancer Hospital, it has been proved that a carcinogenic agent present in tar also belongs to this particular type of chemical compound.

"The gradual elucidation of the structure of cholesterol, vitamin D, and the sex hormones has increased the theoretical importance of the work of Kennaway and his colleagues, since prior to these investigations it might have been argued that the production of tar cancer (first produced by Yamagiwa and Ichikawa, 1915) was of purely academic interest, as the carcinogenic agents apparently bore no relationship to substances taking part in the composition of the body. Their extensive investigations, however, have shown that the carcinogenic hydrocarbons belong to this form of condensed carbon ring compounds, and as has been pointed out by *Cook*, the processes which would be entailed by the formation of the compounds from the naturally occurring sterols and bile acids would involve reduction, dehydration and dehydrogenation and might readily occur in the animal body; it seems possible that these carcinogenics might result from the processes operating upon degradation products of sterol metabolism." (*Cook*, 1933).

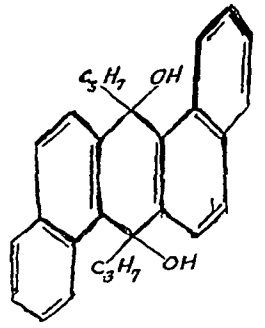


No. 2. 1:2—Benzpyrene

In 1932. Cook, Hieger, Kennaway and Mayneord showed that a series of compounds related to 1:2—benzanthracene possesses carcinogenic properties.

Aschheim and *Hohlweg* determined that in extracts of bituminous material there are estrogenic substances. Recently various investigations have made it probable that "luteal hormones have a similar chemical constitution to the estrogenic hormones."

Cook and *Dodds* and their associates examined a number of hydrocarbons of known carcinogenic character to determine whether they could induce estrus in castrated mice and rats. The first such compound of known chemical structure, which was demonstrated to be estrogenic, is 1-keto 1:2:3:4 tetrahydrophenanthrene. A substance may be both carcinogenic and estrogenic; some that are carcinogenic are not estrogenic, and there are estrogenic substances which are not carcinogenic. Those most active carcinogenically are not the most potent estrogenic compounds.



No. 3. 9:10—Dihydroxy—
9:10—di—n—propyl
9:10—dihydro
1:2:5:6—dibenzanthracene

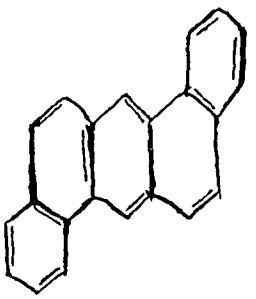
This is the most potent synthetic oestrus-producing agent, obtained by Dodds and is a derivative of 1:2:5:6—dibenzanthracene, the carcinogenic hydrocarbon.

Lacassagne has induced mammary cancer in male mice by injecting estrogenic material ("folliculine"). Only the secondary sex organs, not other portions of the body, are thus affected by ovarian hormones. This specific character distinguishes the action of ovarian hormones from the carcinogenic agents in tar.

Summarizing (*Leo Loeb*) (1), "the carcinogenic hydrocarbons of tar and related compounds, estrogenic substances as well as certain other factors, may cause cancer in those tissues on which they act, but while carcinogenic hydrocarbons as well as regenerative processes (irritation) may affect a great variety of tissues, the estrogenic hormones are limited in their action to the tissues in which they induce growth processes during the normal sexual cycle. Both the hydrocarbons and hormones mentioned

1. Loeb, Leo: Estrogenic Hormones and Carcinogenesis. *J. A. M. A.*, 104:1597, May 4, 1935.

bring about the cancerous transformations of tissues in an indirect manner. They differ in this respect from other agents merely from a quantitative point of view. The mechanism by which ovarian hormones produce proliferative processes in the sex organs differs from the mechanism underlying the cancerous transformation, although the latter may ultimately depend on proliferative processes



No. 4. 1:2:5:6—Dibenzanthracene

acting over a long period of time. There exist, therefore, no direct but only indirect connections between the carcinogenic action of the hydrocarbons of tar and the carcinogenic effect produced by estrogenic hormones."

The foregoing in a brief and necessarily incomplete way indicates the progress being made in this field. Real additions to the knowledge of cancer have been achieved; whether they constitute an important aggregation of blocks in a puzzle picture or are rather coral accretions in relation to the whole problem time must decide.

General. Both American and European literature contains an increasing number of articles favoring the radical abdomino-perineal operation for rectal cancer. *Kirschner* and *Nemec* report doing both the laparotomy and posterior resection synchronously, two surgeons being employed. Voices are raised however in favor of preliminary colostomy and secondary posterior resections and against extending the indications for the more radical operation. As with other radical procedures for cancer elsewhere, the more radical and effective operation may defeat itself by too high a primary mortality, especially in the hands of surgeons having few rectal cancer cases.

As an outstanding authority in the field, *Rankin's* publications merit careful reading, especially those which appear this year in the American Journal of Surgery; Surgery, Gynecology and Obstetrics, and the Proceedings of the Royal Society of Medicine.

Thomas E. Jones' articles on abdomino-perineal resection are worthy of their author, in whom good surgical judgment is combined with finished operative technic. The symposium on rectal cancer in the American Journal of Surgery has contributions by such authorities as Lynch, Jones, Lahey, Binkley, Yeoman, and Barber.

Diagnosis. Fansler and *Anderson* present clearly the matter of diagnosis in the operable stage of the growth and preoperative and post-operative treatment; their gross description of the types of cancer is informative. *Horsley* notes, forcefully, that attention to slight symptoms makes early diagnosis possible. *Meehling* epitomizes the diagnosis and treatment. *Rosser's* further publications on the relation of chronic inflammatory changes to the development of carcinoma contain data which are definite contributions to his subject. He reports 1 fissure, 4 hemorrhoids, 9 fistulae which have undergone carcinomatous change in 2 to 20 years. *Jelks* regards infection, especially that from streptococci, as an important factor in carcinogenesis.

Hayes and Ellis describe the technic of biopsy by needle puncture and aspiration, used in 1400 cases at the Memorial Hospital. Among pathological curiosities and interesting cases noted in clinical reports are the following:

Wakeley reports a case of obstruction from sigmoid cancer with rupture of the cecum.

Jaffe autopsied a case of annular carcinoma of the recto-sigmoid junction with multiple irregular ulcers in the colon above it, which he classified as stercoral ulcers, resulting from the capillary stretching and consequent anaemia in the distended bowel.

Ross' article on carcinoma in youth brings the subject up to date. *Pfeiffer* and *Wood* report a transverse colon cancer in a 7 year old boy.

Smith and *Broders* report 2 cases of melano-epithelioma and 2 of hemangio-endothelioma of the anus; in one of each diagnosis was made only by the tissue examination by the pathologist.

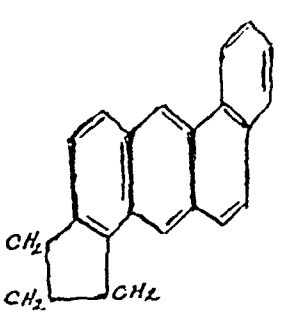
Dixon and *Beaver* report a carcinoma of the rectum treated by fulguration and radium which at autopsy showed no carcinomatous cells in the scar of fulguration and no metastases; death resulted from cerebral embolism. Excised scar tissue in one of *Strauss'* sections shows cancer cells present, in another case they were absent.

Surgical Treatment. Raiford presents an extensive discussion of carcinoma of various segments of the large bowel and reports progress as to operability, 5 year cures and post-operative mortality over a 34 year period; he also reviews the statistics of rectal and anal cancer at Johns Hopkins Hospital.

It seems obvious that no one operation is suitable to all cancers in the middle and upper rectum, to say nothing of those above these sites but still too low for an "obstructive resection" or Miculicz operation, yet this point is lost sight of in some writings.

T. E. Jones continues to favor the one stage radical abdominoperineal resection. *Rankin* prefers the abdomino-perineal method but uses it in two stages perhaps more frequently. Four to six weeks after exploration the colostomy (single barrel) is done, a perineal incision is made to free the rectum up to the peritoneum, the skin closed and laparotomy performed, at which the removal of the rectum and sigmoid is completed. He uses gas-oxygen-ether or ethylene and trans-sacral anesthesia in preference to spinal because of two recent operating room casualties. *Dixon* favors the abdomino-perineal (Miles) procedure where the cancer site permits a choice of method in the higher grades of malignancy, and posterior resection after colostomy for the less malignant growths.

Lahey continues to use his method of fixing the end of the distal segment of the bowel in the abdominal wall, in the midline above the bladder.



No. 5. 5:6—cyclo-Penteno—
1:2—benzanthracene

Gordon-Watson emphasizes the effects of surgical experience on the percentages in operability and mortality statistics. *Gabriel* reports a 20% mortality in 25 one stage abdomino-perineal excisions of the rectum. He restricts perineal excision to very early or very advanced carcinomas of the anus and lower third of the rectum.

Finsterer, O. Goetze, H. Schneider, H. Voelker, M. Kirschner among other Europeans favor abdomino-perineal operation in one or two stages.

Lockhart-Mummery and *H. van Seeman* among others favor preliminary colostomy and secondary posterior resection. *M. Lichtenauer* advocates perineal excision of rectum without colostomy.

The importance of *preliminary preparation* and after care is repeatedly emphasized, viz: (1) Blood transfusion often advisable before operation, more frequently afterward.

(2) The establishment of a satisfactory water balance especially in the dehydrated patient.

(3) The relief of hypoglycemia by free sugar intake.

(4) Evacuation of bowel pre-operatively (repeated enemas; if obstruction absent, cautious catharsis).

(5) Pre-operative opiate medication to quiet peristalsis.

(6) Careful cleansing of the lower loop before second stage of two stage operation.

(7) Some method of peritoneal vaccination is used by a number of surgeons; its value is questioned by others.

Irradiation Therapy. Irradiation treatment continues a palliative measure but as radiosensitivity and dosage become better known the indications for its use as a curative agent are advanced by some experienced therapists. *Bowing* and *Fricke* report 500 cases and feel that the higher grades of malignancy especially, require irradiation.

The British Medical Journal Annotations note that low voltage X-ray therapy as used by *Chaoul* in Germany may obtain results to compare favorably with the radium bomb. *Binkley* records his results with a technic consisting of pelvic radiation with a maximum skin dosage through 6 or 7 portals of entry, given daily for 3 weeks. In proper cases 1-3 millicuries of gold screened radon needles are implanted per rectum, 2 weeks later. Further treatment is advisable at a later period in some cases. Palliation only is sought in the advanced (inoperable) cases; curative results may ensue in the selected early cases.

Max Cutler states the decision between operation and irradiation is at times difficult, such decision is based on 2 factors: operability and radiosensitivity. The clinical signs of operability are often fallacious, the extent of the disease may be impossible to determine by clinical examination. Radiosensitivity does not necessarily mean curability nor (to a less extent, Ed.) does radioresistance mean incurability.

Electrocoagulation. Strauss used electro-coagulation of the tumor in 42 patients, 20 having a colostomy done. He feels the results justify the continuance of this form of treatment. He states the results compare favorably with radical excision and half of the group escaped a colostomy.

Thorek states that inoperable cases may be benefited and life prolonged by electro-coagulation of the tumor and proctotomy.

Chemotherapy. Bargen concludes that colloidal lead phosphate given intravenously to a degree of lead intoxication possesses value.

Murray gives a critical review of the selenide treatment of cancer. *Körbler* in Germany and several South American authors favor the use of snake venom for its inhibitory effect on cancer and especially to relieve pain. Others deny its value.

To those who wish to follow the subject of cancer closely the Abstracts in the American Journal of Cancer; and Surgery, Gynecology and Obstetrics will prove valuable.

SECTION VIII—*Editorial*

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastroenterological Association is in no way responsible for editorial expressions.

CERTAIN PERTINENT OBSERVATIONS UPON MILK AND CHOLESTEROL AS THEY RELATE TO INFECTION AND TO ARTERIOSCLEROSIS

SINCE the publication of my review on "Milk" (*) as well as the editorial on "Cholesterol" (**) in this Journal, developments of such importance have occurred that I am impelled again to direct attention to these topics.

MILK

First, I wish to emphasize the tremendous consequences of the *infectious elements that are carried by milk.* Prof. Lloyd Arnold (1) believes that I am unduly alarmed about the milk problem and that pasteurized milk is safe and wholesome. He calls attention to the fact "that the dorsum of the tongue contains a rich endogenous bacterial flora and that sterile milk will not be sterile when it passes through the oral cavity." Why then should we not continue to feed raw milk and not trouble to pasteurize it, or bother about infectious elements carried in other foods? No, like all milk bacteriologists, Dr. Arnold relies upon the *total* bacterial count and has the ideal of pasteurization constantly before him. Pasteurization at best is but an ideal procedure. Dr. Arnold realizes that it is rarely carried out as planned or theoretically considered proper. Even when so conducted, pasteurization does not kill all the pathogenic bacteria. This has been well demonstrated in the epidemic of bovine tuberculosis in Great Britain, where "over the counter" milk was found frequently to be contaminated. *It is imperative that the bacteriologist follow this method of examination and study the milk for pathogenic bacteria as it comes to the consumer.*

However, Dr. Arnold's contribution revealing the bacterial content of the lingual mucosa is of great value. The tongue may act as a focus of infection. It is a rule in my Clinic to advise swabbing the tongue with a ten per cent mercurochrome solution during the treatment of infectious diseases particularly of ulcerative colitis, gastric and duodenal ulcer, gall bladder disease, etc.

As an illustration of the tremendous influence of the propaganda for the increased consumption of milk, I cite the fact that two bacteriologists whom I attempted to induce to engage in the bacteriologic study

*"Milk"—Horace W. Soper, M.D.: *Am. Jour. Dig. Dis. and Nutr.*, Vol. 11, No. 2, p. 113.

**"Cholesterol"—Horace W. Soper, M.D.: *Am. Jour. Dig. Dis. and Nutr.*, August, 1935.

of milk as it is received by the consumer, refused to do so on the grounds that they would do nothing that might impair the confidence of the public in milk as a food!

G. M. Fyfe (2), health officer for St. Andrews, England, in his annual report, says that about forty per cent of the cows in that country are infected with tuberculosis. Scoville (3) states that mild ambulatory cases of *Brucella abortus* infection in man are common and frequently not diagnosed. Angle (4) calls attention to the tremendous increase of *Brucellosis* in this country. He finds that 9965 cases were reported to January, 1935, and concludes that the correct diagnosis is never made in many of the cases.

Minnett (5) discusses *"the widely prevalent and well recognized chronic form of streptococcus mastitis existing in our herds"* and directs attention to an acute streptococcus mastitis of such severity that partial destruction of the udder occurs. Swift, Langfield and Goodner (6) present a table of the various groups of hemolytic streptococci. In their Group "A" they refer particularly to cattle affected with mastitis and to the human infections, such as scarlet fever, puerperal sepsis, erysipelas, septic sore throat, pneumonia, etc. They state, "When, therefore, members of (the hemolytic streptococci group) are found in milk, the inference to be drawn is either that the cows furnishing the milk have mastitis due to a Group A streptococcus, or that the milk has become contaminated from a sick man or from a human carrier. It seems probable, therefore, that any milk in which Group A hemolytic streptococci are found is unfit for human consumption. Probably the presence of strains other than Group A in the throat, intestine or vagina of human beings arises from the consumption of milk or other food products containing them."

Geiger, *et al* (7), in "Food Poisoning from Ice Cream," conclude that "since the lower temperatures used in ordinary refrigeration and ice-cream freezing have only growth-*inhibiting* and not bacteria-*destroying* power, and since milk and milk food products, because of their inherent character, offer excellent bacterial culture medium possibilities, ice-cream and other milk food products should be subject to rigorous standards in production, processing and marketing, with the provision of every reasonable safeguard to the public health."

The above facts cannot be dismissed with a wave of the bacteriologic hand and the statement that "the organisms found were not proved to be pathogenic for man." Clinical experience teaches us that the canned evaporated milk is safe, contains all the essential nutritive elements, and cannot remain on the dorsum of the tongue long enough for propagation of the bacteria.

Clinicians are not concerned about the 75% or 90% of individuals who establish an immunity against streptococcus or tuberculous infection, but *are* interested in the smaller percentage of mankind who are susceptible. Milk is undoubtedly the chief agency for the dissemination of the streptococcus. Where did *this* case of *S. viridans* originate? Why does such a large percentage of school children develop infected tonsils? Where did *this* patient acquire septic sore throat? Why is the increase of dental caries in children concomitant with the augmented consumption of milk? Such are questions constantly arising in practice; they require definite answers.

Probably man has employed milk as a food for over 6000 years according to his drawings on cave walls. His use of the herd unquestionably marked the dawn of community life and laid the foundations of modern civilization.

Since the vitamine theory originated by McCollum, the propaganda for the larger use of milk in our dietary has been so active that nearly all students of nutrition are obsessed by it. What are the biological inferences?

1. All mammals, excepting the human, cease the use of milk as a food after weaning. The mother's mammary gland remains quiescent until activated by parturition.

2. The dairy cow, stimulated and bred to yield milk over a long period of time, develops hypertrophy of the mammary gland. She is frequently found to be infected with a low grade streptococcus mastitis. Efforts to disinfect the udder often cause a chronic eczema; crusts and scales fall into the milk.

3. Milk is such a good culture medium that it is frequently contaminated by infectious agents not originating in the cow. "Bacterial soup" is a good synonym for milk.

4. As a result of his violation of a primary biologic law, Man has been severely penalized by the host of infectious diseases that are disseminated by milk.

I am aware of the magnitude of the problems involved and my object in this presentation is to stimulate further study and criticism of milk as it reaches the consumer.

CHOLESTEROL

In my first communication, I directed attention to the clinical significance of the subject, relying especially on the work of Leary (8), Joslin (9), Rabinowitch (10), Hartung and Brüger (11), Lockie and Hubbard (12). Since that time numerous important contributions have been made to the current literature.

Moschcowitz (13) contests the theory of the metabolic origin of arteriosclerosis. He asserts that simultaneous arteriosclerosis in the pulmonary and general circulation rarely occurs and that the relation of intravascular tension in the causation of arteriosclerosis is vital in the study of the problem.

In reply to Moschcowitz, Leary (14), states that he has shown that the lesions of human atherosclerosis owe their variety to the relative ability of the cells in these lesions to metabolize cholesterol. In youth this power is great, in middle life the metabolism is slow and scarring results. In old age, the cells cease to function and "atheromatous abscesses" are responsible for the selective localization and degree of the lesions. Basically, atherosclerosis is dependent for its causation in disturbances in the cholesterol metabolism.

Joslin, Warren and Root (15) also reply to Moschcowitz, taking exception to his statements "that all evidence seems to show that arteriosclerosis is the cause of diabetes rather than the reverse," and "when diabetes occurs in arteriosclerosis, the inference is that the capillaries of the islands of Langerhans are affected." They point out that at least 10% of all cases of diabetes begin in the first two decades of life without any evidence of the existence of arteriosclerosis and that persons with diabetes of long duration show more arteriosclerosis in the legs and heart than do

non-diabetic persons. Many cases of diabetes at autopsy show little or no arteriosclerosis of the pancreatic vessels even though vascular damage elsewhere is severe.

Brenner (16) states "that pulmonary vascular sclerosis increases in frequency and severity with the age of the patient. It is practically as common as systemic vascular sclerosis and is constant in patients over forty."

Many clinical articles, too numerous to mention here, have appeared recording the good effects produced in vascular disease by a sharp limitation of the cholesterol content of the diet. I personally can confirm the good results produced by this method even in advanced severe cases of vascular disease affecting the cerebral and coronary vessels. For years I employed an "alkaline ash" regimen, which was in reality a diet with small cholesterol content. Sansum, in a personal communication, states that his clinical experience has been identical with mine when employing the same dietary regimes. Space forbids publishing case records here but I hope to do so in the near future. Such dietary formulae are not easy to follow. The whole art of modern cookery is in a conspiracy against it. The chief articles to avoid are eggs, cream, butter, pork fat, and the solid internal organs, as liver, sweetbreads, etc. Nearly all muffins and desserts are milk, cream, butter and egg concoctions.

Experimental work in cholesterol metabolism has demonstrated the great value of thyroid as well as iodine as controlling agents or lipoid solvents. I can verify the efficacy of their employment, clinically, in selected cases.

The evidence appears to justify the statement that hypothyroidism is usually associated with a poor cholesterol metabolism, which would account for the tendency of individuals of this type to develop *obesity, gall stones, gout, degenerative arthritis* and *cataract.*

More chemical work on food stuffs is necessary particularly in regard to the vegetable oils. More intense clinical study is highly desirable so that we may control the intake of cholesterol with more exactness.

We know that cholesterol is a necessary constituent of the body cells, but enough evidence has accumulated to the effect that an excess in the diet may be extremely injurious especially to the adult after fifty.

The clinician of today should be both milk minded and cholesterol conscious, not only in the treatment of disease but in the realm of Preventive Medicine.

Horace W. Soper, St. Louis.

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SECTION XI—*Societies, Programs and Proceedings*

Program of the Thirty-Ninth Annual Meeting of the American Gastro-Enterological Association

MAY THE 4TH AND 5TH, 1936
HOTEL CLARIDGE
ATLANTIC CITY, N. J.

MONDAY, MAY 4, 1936

MORNING SESSION, 9:00 A. M.
Daylight Saving Time

MEMORIAL ADDRESSES
of

Dr. John Bryant by Dr. Franklin W. White
Dr. Lafayette B. Mendel by Dr. Victor C. Myers
Dr. Henry W. Bettmann by Dr. Leon Schiff
Dr. George W. McCaskey by Dr. William Gerry Morgan

PRESIDENTIAL ADDRESS
Dr. Howard F. Shattuck, New York, N. Y.

1. "Cholesterol Metabolism in Jaundice"
   Dr. S. Allen Wilkinson, Boston, Mass.
   Discussion to be opened by Dr. Andrew C. Ivy, Chicago, Ill.

2. "Biliary Stasis"
   Dr. Carl H. Greene, Brooklyn, N. Y.
   Dr. J. Russell Twiss, New York, N. Y.
   Dr. R. Franklin Carter, (by invitation), New York, N. Y.
   Discussion to be opened by Dr. Charles Gordon Heyd, New York, N. Y.

3. "The Prognosis of Acute Hepatic Insufficiency"
   Dr. Chester Jones, Boston, Mass.
   Discussion to be opened by Dr. H. L. Bockus, Philadelphia, Pa.

4. "Chronic Hepatitis with Jaundice (Biliary Cirhosis)"
   Dr. James F. Weir
   Dr. Albert M. Snell, Rochester, Minn.
   Discussion to be opened by Dr. David Riesman, Philadelphia, Pa.

5. "Macrocytic Anemia in Diseases of the Liver"
   Dr. David H. Rosenberg, Chicago, Ill.
   Discussion to be opened by Dr. M. M. Wintrobe, (by invitation), Baltimore, Md.

THE ALVAREZ LECTURE

Founded in 1929 by Dr. Frank Smithies

"THE DIGESTIVE TRACT IN ANEMIA"

Dr. George R. Minot, Professor of Medicine, Harvard University, Boston, Mass.

Adjournment for Luncheon

2:30 P. M.

6. "Miscellaneous Observations on Intubation of the Small Intestine"
   Dr. T. Grier Miller
   Dr. W. Osler Abbott
   Dr. Walter G. Karr, (by invitation), Philadelphia, Pa.
   Discussion to be opened by Dr. Max Einhorn, New York, N. Y.

7. "Surgical Aspects of Regional Ileitis"
   Dr. A. A. Berg, New York, N. Y.
   Discussion to be opened by Dr. Sara M. Jordan, Boston, Mass.

8. "The Components of Gastric Secretion"
   Dr. Franklin Hollander, (by invitation), New York, N. Y.
   Discussion to be opened by Dr. Walter C. Alvarez, Rochester, Minn.

9. "Gastric Secretory Behavior in Chronic Gastritis"
   Dr. H. L. Bockus
   Dr. J. F. Monaghan, (by invitation)
   Dr. Karl Kornbloom, (by invitation), Philadelphia, Pa.
   Dr. George R. Moffitt, (by invitation), Harrisburg, Pa.
   Discussion to be opened by Dr. Burrill B. Crohn, New York, N. Y.

EXECUTIVE SESSION

(Associate members are requested not to attend)

ANNUAL DINNER, 7:30 P. M.

HOTEL CLARIDGE, ATLANTIC CITY, N. J.

Guest of Honor

Dr. William Mather Lewis, President, Lafayette College, Easton, Penn.

"The Cultural Background of the Professional Man in Medicine"

TUESDAY, MAY 5TH, 1936

MORNING SESSION, 9:30 A. M.

10. "Further Experimental Studies on the Etiology of Ulcerative Colitis: The Possible Virus Factor"
    Dr. Moses Paulson, Baltimore, Md.
    Discussion to be opened by Dr. Heinrich Necheles, Chicago, Ill.

11. "The Diagnostic Significance of Anti-Dysentery Bacteriophage"
    Dr. T. T. Mackie, New York, N. Y.
    Discussion to be opened by Dr. Morris L. Rakieten, (by invitation), Brooklyn, N. Y.

12. "Symposium on the Pancreas"
    Physiological Aspects: Dr. Andrew C. Ivy, Chicago, Ill.
    Pathological Aspects: Dr. William G. MacCallum, (by invitation), Baltimore, Md.
    Medical Aspects: Dr. Thomas R. Brown, Baltimore, Md.
    Surgical Aspects: Dr. Daniel F. Jones, (by invitation), Boston, Mass.
    Discussion to be opened by Dr. Joseph H. Pratt, (by invitation), Boston, Mass.

13. "Report of Special Committee on Enzymes"
    Dr. A. H. Aaron, Chairman, Buffalo, N. Y.

Adjournment for Luncheon

2:00 P. M.

14. "Hypoglycemia—A Clinical Survey of Four Hundred Cases Having This Common Finding"
    Dr. Lay Martin, Baltimore, Md.
    Dr. George A. Hellmuth, (by invitation), Baltimore, Md.
    Discussion to be opened by Dr. Victor C. Myers, Cleveland, Ohio.

15. "Thoracic Stomach and Diaphragmatic Hernia"
    Dr. Leon Bloch
    Dr. A. M. Serby, (by invitation)
    Dr. Samuel Salinger, (by invitation), Chicago, Ill.
    Discussion to be opened by Dr. Dewitt Stetten, New York, N. Y.

16. "Specific Food Sensitiveness"
    Dr. Walter Alvarez, Rochester, Minn.
    Discussion to be opened by Dr. Arthur F. Coca, (by invitation), New York, N. Y.

17. "A Consideration of Some of the Newer Methods for the Treatment of Peptic Ulcer"
    Dr. Andrew B. Rivers, Rochester, Minn.
    Discussion to be opened by Dr. Walter L. Palmer, Chicago, Ill.

8. "Ulcerating Gastric Neoplasms and Their Differentiation from Simple Benign Ulcers, Roentgenological and Pathological Criteria"
Dr. Lewis Gregory Cole, New York, N. Y.
Discussion to be opened by Dr. Frank W. Konzelmann, (by invitation), Philadelphia, Pa

The following papers will be read by title.

"Studies in Gastric Pepsin"
Dr. Frances R Vanzant, Houston, Texas.

"Cystadenomata of the Pancreas: A Surgical Report"
Dr. R. Franklin Carter, (by invitation), New York, N. Y.
Dr. Lewis Slattery, (by invitation), New York, N. Y.

"The Changes Within the Cells of the Gastric Mucosa During Secretory Activity"
Dr. A. J. Gitlitz, (by invitation), New York, N. Y.
Dr. W. Levison, (by invitation), New York, N. Y.

IN MEMORIAM

Ivan Petrovich Pavlov
1849 — 1936

AFTER a full lifetime of extraordinary scientific achievement, and having recently been the central figure of the International Neurological Congress in London and the International Physiological Congress in Leningrad and Moscow, Ivan Petrovich Pavlov died on February 27, at the age of 86.



A photograph of Pavlov taken August 8, 1935.

He was born on September 26, 1849, the son of a poor priest. Being led to abandon a theological education by the stimulus of G. H. Lewes' *The Physiology of Common Life*, he entered the University of St Petersburg (1871) and there came into contact with von Cyon, a brilliant thinker and an expert in physiologic methodology, and the talented chemist Mendeleef. He became a collaborator with Cyon in 1874 and an assistant in 1875 under whom with Afanasiev he did his first investigation on the pancreatic nerves. After completing the medical course in the Military Academy in 1878 or 1879, he was granted a fellowship in the research laboratory of Botkin, an internist, which enabled him to continue in research and to complete his thesis for the M.D. degree in 1883. His thesis described, independently of Gaskell, the nervous control of the heart. He then studied for two years (1884-86) under the Wylie fellowship with Ludwig and Heidenhain in Germany. On returning to St Petersburg he again worked in Botkin's laboratory, his chief research interest from 1878 to 1888 being the circulatory system. In 1890 he was appointed Professor of Pharmacology at the Military Medical Academy in St. Petersburg, a position he retained until 1924 However, in 1891 he was also appointed director of the department of physiology in the newly built Institute of Experimental Medicine where he started and did most of his work on the digestive glands and had the opportunity of taking full advantage of the recently developed technique of aseptic surgery and of making a detailed exploration of the gastro-intestinal tract by the production of "chronic" fistulae in animals. His classical monograph, *The Work of the Digestive Glands*, appeared in 1897 and constitutes, figuratively, the "Old Testament" of digestive physiology. The English edition, which appeared in 1910,

represents the research achievements of Pavlov and his entire laboratory staff from the period of about 1888 to 1904. For this work he undeniably merited and received the Nobel prize in 1904. In 1902 being impressed by his observations on the "psychic" secretion of saliva, gastric and pancreatic juice, the direction of his research changed. Subsequently, he devoted his entire attention to a study of processes in the central nervous system by the method of conditioned reflexes.

It is idle to review those magnificent studies on the higher reflex mechanisms which are so well known and which form the groundwork of any comprehension of central nervous system activity. And, a further appreciation can add little to his dominant and secure place as one of the foremost benefactors of science and human endeavor. Pavlov, the man, was characterized by a single minded devotion to his science. During the rigors of the revolution, when without heat or light, his only complaint was of having to spend six hours each day guarding the firewood stacked outside the Academy. He was no stranger to hard work. In his earlier experiments the operated animals were tended by his wife and himself in their own home. A man of great intellect, scientific honesty, and gentlemanly simplicity, it is fortunate for the world that he was permitted a long and useful life.

Andrew Conway Ivy,
Northwestern University, Chicago.

SECTION XII—*"The Clinic"*

Gastric Carcinoma

Necessity for Earlier Diagnosis as Shown by Case Reports

By

B. MARKOWITZ, M.D.
BLOOMINGTON, ILLINOIS
and
M. D. MOLAY, M.D.
CHICAGO, ILLINOIS

CARCINOMA of the stomach is one of the most frequent offenders in producing a discrepancy between the pathological and clinical findings. Often the history indicates a gastric upset dating back only 3 or 4 weeks and at operation an extensive inoperable carcinoma is found. The contradictory findings may in many instances be explained by the following: 1. Early gastric cancer does not give the classical symptoms characteristic of the disease as described in text books and 2.—the great variety of forms in which gastric carcinoma presents itself is not made sufficiently familiar to the average physician. MacCarty[1] reports that not over 25% of the gastro-intestinal cancers coming to the Mayo Clinic had previously been X-rayed and 75% of these cases are inoperable and hopeless when first seen at the clinic. In a small series of gastro-intestinal malignancies we[2] have previously reported 70% so far advanced that only biopsy and palliative surgery could be done.

"CLASSICAL" SYMPTOMS

Classical symptoms such as constant and definite pain, constant motor function incompetency, and definite palpable tumor mass are frequently absent and certainly lose their classical distinction, if a series of gastric cancers is studied.

It is the common opinion that pain is constant, dull and aching in type; yet frequently we receive a half or even more than one-half of a resected malignant stomach in which the history of pain was not of the orthodox dull and aching type or paradoxically enough may have been completely absent. Gaither[3] in reviewing 245 cases of gastric cancer comes to the conclusion that there is no characteristic cancer pain and he feels that a consideration of the character of pain is of negligible importance.

Constant motor function incompetency would strangely enough be a highly desirable finding. In the greater number of instances it means a certain degree of pyloric block, which if the progress is rapid, would force the patient to seek early medical advice. Unfortunately, however, we often receive a carcinoma involving a large part of the stomach and the history reveals that there was no motor function incompetency. This is especially true when the tumor involves those areas in which the passageway is not directly obstructed as the cardia or the lesser curvature. In addition there is the infiltrating type of carcinoma which invades the submucosa and deeper structures and involves most of or all of the stomach with no obstruction. On the other hand, benign polyposis of the stomach may produce a motor function incompetency. The question may be raised, "How often do we find carcinoma associated with polyposis of the stomach?" Benedict and Allen[4] report adenomatous polypi of the stomach as potential malignancies in 41% of the cases, while Jaffe[5] reports that in 100 cases

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of gastric carcinoma autopsied only 7 revealed polypi. He adds however "It is possible, however, that as the tumor grows the polypi are enveloped in the overgrowth and thus obscured."

Similarly we cannot lay too much emphasis upon the presence or size of a definite tumor mass. In certain cases physical and X-ray examination fail to reveal the presence of carcinomatous lesions especially those in the cardia which are later found at operation or post mortem. In other instances the interpretation of the size of the lesion does not correspond favorably with the actual tumor mass found. Nor can the type of onset and time of existence of such a tumor be placed in any definite category. In going over the histories of many of these cases in which large gastric carcinomas were resected, one can easily be convinced that it is possible for such a cancer with ulcer type of history to have existed as a primary malignancy for three to five years. Neither is it difficult to believe that the symyptoms in such cases may be sudden in their onset. Not infrequently we examine a pathological specimen of a large resected gastric carcinoma, the history of which indicates an abrupt rather than a gradual onset.

Just as the time element may be irregular in diagnosis so may the recurrance of such a tumor be irregular in prognosis. The histological structure cannot always settle the prognosis as well as it does the diagnosis. Even the diagnosis of a very early carcinomatous degeneration of an ulcer can be missed and surely the question of recurrence cannot often be definitely settled by the microscopical picture. We have all seen rather malignant forms of cancer which did not recur or recurred after a lapse of years while malignancies of lesser degree recurred rather early. It happens much too often that after a long period of belief in a cancer cure, recurrence is found.

VARIETY OF FORMS OF GASTRIC CANCER

The forms of gastric cancer pertinent to this discussion are those which do not follow the orthodox course as described in text books; particularly those cases in which the symptoms do not point definitely to a gastric disturbance and the diagnosis is established at post mortem examination. Stebbins and Carns[6] recently described a case of thrombocytopenic purpura associated with adenocarcinoma of the stomach in a young adult in which the carcinoma was neither suspected nor found until post mortem examination. In this case the age, too, is somewhat unorthodox; although untold numbers of gastro-intestinal cancers of the young have been reported, yet it is necessary to call the general practitioner's attention to the fact that malignancies of the stomach and intestines not infrequently occur in the young adult notwithstanding the cancer-age spoken of in text books (7).

CASES

The following case histories illustrate the various forms of gastric carcinoma which present symptoms of other ailments:

Case I: A white male, 51 years of age, complained of general abdominal discomfort and vague epigastric pain over a period of 8 months. Occasionally he was nauseated and vomiting gave some relief. His appetite was poor and he had lost 20 pounds during the past 3 months.

On *examination* he was somewhat emaciated and his skin was pale and somewhat sallow. The heart and lungs were negative; the liver was not palpable, the spleen was slightly enlarged; he ran a continous low grade temperature between 99° F. and 99.8° F.

Laboratory examination revealed: R.B.C. 1,920,000; W.B.C. 4,500; Hemaglobin 48%; marked poikilocytosis and disproportion in size of red cells many of which were more than twice the normal size; no immature forms were found; *icteric index* was reported as 10; *Benzidine test* on stools strongly positive; an Ewald test meal showed 48° total acidity and 18° free hydrochloric and positive occult blood test. *X-ray examination* was negative except for the suggestion of a decreased pyloric diameter; this was not considered a deformity.

The *clinical diagnosis* rested between a primary anemia and carcinoma of the stomach. Despite transfusions, liver therapy and supportive measures, the patient ran a very rapid down-hill course and died 10 months after the onset of complaints.

At post mortem one was immediately struck with the pale anemic appearance of all the organs. The heart was normal in weight (305 grams) and in appearance. The lungs were congested, otherwise normal. The spleen was slightly enlarged, (205 grams) soft and the pulp was purple red. The liver appeared normal (2,000 grams). The essential findings were in the stomach. Its walls, especially at the pyloric end were thick and leathery, the cut surface was light gray and gristle-like. The mucosa was pale and with the exception of several small plaques in the pre-pyloric region, quite smooth. The perigastric lymph glands were all enlarged, firm and gray. *Microscopic examination* of the stomach wall and lymph glands confirmed the gross diagnosis of a scirrhous carcinoma.

The combination of symptomless carcinomas of the stomach and severe anemia is not infrequently found at the post mortem table. Such anemia may even present hematological findings of pernicious anemia and in the absence of definite gastric symptoms may present the picture of a primary anemia (7).

Case II. A well developed, rather obese female, 41 years of age, gave the history of having been entirely free from any digestive disturbance up until two months before examination. At that time she was seized with sudden cramp-like pain in the "pit of the stomach" which lasted several hours and was followed by a spell of vomiting and diarrhea. Since this first onset she had had two or three milder attacks neither of which was very severe. Vomiting however occurred quite frequently and the pain was described as "just everywhere over the abdomen."

On *examination* the temperature was elevated about one degree, the skin was slightly icteric and a tender mass was palpable in the middle upper abdomen just to the left of the midline. The liver and spleen were not palpable and all other findings were negative. Laboratory examination revealed 18,500 W.B.C. with 72% polynuclear cells, an icteric index of 22 and an Ewald test showed 42° total and 22° free hydrochloric acid. *Upon X-ray examination* there was an unexplained defect in the cardia of the stomach. Negative findings in the intestines and "no visualization" of the gall bladder were reported.

The patient was considered a surgical case with ruptured gall bladder and retrogastric abscess or pancreatic abscess as the most likely diagnosis. At operation a large abscess was found in the lesser peritoneal cavity. Despite drainage and supportive measures including transfusions the patient died on the third post operative day. At post mortem examination the essential pathology was an ulcerating adenocarcinoma of the greater curvature of the stomach which had perforated through the meso-colon with abscess formation.

Cancers of the cardia of the stomach are comparatively rare (about 10%) and are rather difficult to diagnosis. Found in this area, which is termed a

silent area, the lesion produces very few symptoms because no obstruction results.

CONCLUSIONS

In reviewing any large number of cases it will be found that early cancerous lesions of the stomach present no typically definite symptoms and that those listed in our books are those exhibiting symptoms of advanced malignancy; that gastric carcinoma at times manifests itself in atypical forms. For these reasons it is necessary to revaluate the symptoms and clinical histories for teaching purposes. Such teaching that symptoms are always gradual, that pain is always constant and dull, that a mass is always palpable, that weight loss is an extremely important factor and that there is a definite cancer age should be modified in face of repeated contradictory post mortem findings. Instead, stress should be placed upon finding the early gastric cancer by suspecting every case of continuous gastric distress as a potential malignancy until proved otherwise.

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ABSTRACTS

CLINICAL MEDICINE

JONES, CHESTER M., BENEDICT, E. B., AND HAMPTON, A. O.

Variations in the Gastric Mucosa in Pernicious Anemia: Gastroscopic, Surgical and Roentgenologic Observations. Am. Jour. Med. Sci., Nov. 1935, p. 596.

Apparently there are histologic changes in the gastric mucoca which are invariably associated with pernicious anemia. These changes consist in a diffuse inflammatory process leading to atrophy of the gastric glands, most striking in the cardia and decreasing in severity toward the pyloric end of the stomach. Henning is quoted as having found diffuse atrophy of the mucous membrane in all cases of pernicious anemia, in many cases of complete achylia and carcinoma of the stomach. The color of the mucous membrane is grayish yellow or grayish green. (The color of normal gastric mucous membrane is red) (the Authors' note).

The purpose of the authors was to study the stomach mucosa endoscopically during relapses and remissions in pernicious anemia and contrast the two. Five cases are reported in complete and exhaustive detail. One during his illness had a gastric hemorrhage and at operation a small adeno-carcinoma of the greater curvature was found and removed. The man recovered and gastroscopy in March 1935 showed slight hypertrophy of the mucosa without polypus or metastases.

Patient 2 had pernicious anemia with gallstones which were removed together with two polypoid tumors of the stomach. Hypertrophic gastritis was found. The operation was done during a remission following intensive parenteral liver therapy. The polypi which were removed were subsequently pronounced adeno-carcinoma. Two months later the patient was vastly improved and gastroscopy showed a mucous membrane of normal color with apparently normal gastric markings.

Patient 3 was diagnosticated as pernicious anemia and X-ray showed an irregular filling defect in the lower half of the stomach which was thought to be carcinoma. The gastric contents with histamine showed anacidity. Gastroscopy showed a very pale, thin mucous membrane throughout the entire stomach. On the lesser curvature and posterior wall of the antrum there was a rounded elevated red tumor which on later operation was found to be a long polyp ulcerated in two places. It was benign. The patient convalesced but later relapsed because his treatment was not continued. Gastroscopy revealed a chronic gastritis. Treatment for pernicious anemia was re-established and two months later gastroscopy showed a mucosa which was of normal color with no apparent atrophy.

Patient 4, a woman, aged 70, showed gastric contents with some blood and no free HCl. A diagnosis of pernicious anemia and gastric polyposis was made. At operation several months later when her R.B.C. count was 5,500,000 and hgb. 90%, the mucosa of the stomach was found covered with small polyps; one three inches in diameter. Six years later the patient felt well on the ingestion of liver and gastroscopy revealed what was thought to be nearly a normal appearance of the stomach.

Patient 5, white man, aged 46 was found with pernicious anemia and a pale gastric mucosa of an atrophic gastritis with probable pseudo-polyposis. Intensive liver therapy was instituted and two months later the color of the gastric mucosa was practically normal, though somewhat granular in places. On the greater curvature there was a small smooth swelling which might have been a polyp.

The authors found by repeated examinations of the gastric contents in the patients exhibiting improved mucosal conditions under treatment that there was no return of hydrochloric acid where previously achlorhydria had been present.

In the summary of this admirable publication the authors state that following specific therapy of the pernicious anemia evidences of atrophy and hypertrophy of the stomach have both tended to disappear, and that the change from an appearance of atrophy represents an epithelial change associated with successful treatment of a specific deficiency state, rather than the healing of a chronic inflammatory process; whereas a return to normal from a grossly hypertrophic condition of the gastric mucosa represents a subsidence of a chronic gastritis.

Allen Jones, Buffalo

INGEGNO, ALFRED P.

The Elevated Blood Urea of Acute Gastro-Intestinal Hemorrhage and its Significance. Am. Jour. Med. Sci., Dec. 1935, p. 770.

Forty-two cases of hemorrhage due to peptic ulcer are reported and the cases divided into two groups—1, including 17 cases with blood urea of over 38 mgms. and another group of 25 cases with blood urea less than 38 mgms. There were no deaths in either group. Neither sex nor age seemed significant nor was there noticeable correlation between the azotemia and the degree of anemia present. High blood nitrogen figures were almost exclusively found in those in whose blood

samples were taken within three days of the acute episode.

High blood urea nitrogen probably depends upon sudden loss of blood, shock, dehydration and the absorption of nitrogen from the blood in the gastrointestinal tract.

The azotemia probably plays little part in the clinical symptomatology in uncomplicated cases. In cases with hepatic cirrhosis, diabetes or nephritis gastrointestinal hemorrhage may precipitate a very serious or fatal syndrome.

The author concludes:

1. In cases of acute gastrointestinal hemorrhage studied within three days of the occurrence of the hemorrhage, there is an elevation of the blood urea above normal. This is probably due to the nitrogen intake represented by the protein of the blood retained in the gastrointestinal tract, plus the factors of hemorrhage, per se. shock, dehydration and starvation.

2. In complicated cases this azotemia does not reach uremic proportions and plays little, if any, part in the symptomatology.

3. In cases with continuing hemorrhage the elevated urea persists or increases and points to an unfavorable outcome.

Allen Jones, Buffalo.

CROHN, BURRILL B., AND ROSENAK, BERNARD D.

A Combined Form of Ileitis and Colitis. J. A. M. A., Jan. 4, 1936, Vol. 106, p. 1.

Granulomatous, ulcerating and stenosing inflammation of the small intestine was described by Crohn, Ginzberg, Leon and Openheimer in 1932, and was called regional or terminal ileitis. Later Harris, Bell and Brunn described an identical process in the jejunum, a jejunitis, or regional enteritis.

Another addition to the aforementioned conditions is now described, namely a terminal ileitis accompanied by a simultaneous inflammatory and ulcerative colitis. The clinical manifestations of this disease, which usually occurs in young people, are abdominal pain, nausea and vomiting, mild diarrhea with occasional bloody stools, loss of weight, night sweats and fever going as high as 103 degrees F.

In all the cases presented, there was a typical ileitis and colitis. In some cases the colitis was continuous with the ileitis, while in others it was patchy.

The diagnosis rests on careful roentgenographic studies both by barium sulfate meal and enema.

Treatment is by colostomy and removal of the diseased ileum and sometimes the involved colon, followed by ileotransverse colostomy or ileosigmoidostomy.

Francis D. Murphy, Milwaukee.

EQUEN, MURDOCK.

"Esophageal Obstruction: Diagnosis and Treatment." South. Med. Journ., 28:1103-1107, Dec. 1935.

Esophogeal obstruction may be due to extrinsic or intrinsic causes. Extrinsic causes include retropharyngeal and peritonsillar abscesses, direct infiltration by carcinoma of thyroid, larynx or other neighboring structures, retrotracheal or substernal adenoma of the thyroid, tumor of the mediastinum, and aneurysm of the arch or other anomalies of the aorta.

The most common intrinsic cause is benign cicatricial stenosis resulting from the swallowing of caustics. Frequently, there is more than one stricture. The best treatment is immediate gastrostomy followed after the inflammatory process has subsided by retrograde dilatation. While foreign bodies rarely are causative factors, the history of swallowing one should always be seriously considered when obtained. Another cause of obstruction is cancer. Although it may be easily diagnosed, and is of slow growth and late metastasis, it is invariably fatal because of late diagnosis. Diverticulum is another cause not recognized as early as it should be. Suggestive early symptoms are a sense of irritation or of foreign material in the throat and an increase in mucus. Just after the patient takes a drink of water, sudden pressure over the diverticulum forces the water back into the mouth with the production of a gurgling noise. The most common diagnostic symptom of cardiospasm is the regurgitation of food which has not been acidified, although the patient usually believes he is vomiting. Peptic ulcer of the esophagus should be suggested by pain in swallowing. Congenital anomalies include the opening of the esophagus into the posterior wall of the trachea and a persistent shortening of an otherwise normal esophagus.

Any person who complains of difficulty in swallowing should have a careful history, physical, X-ray, and serological examination. If the diagnosis is not then established, esophagoscopic examination with biopsy where indicated, should be done.

The hope is expressed that every hospital will be equipped with specialists and instruments necessary for bronchoscopic or esophagoscopic examinations, as they now are for cystoscopic work.

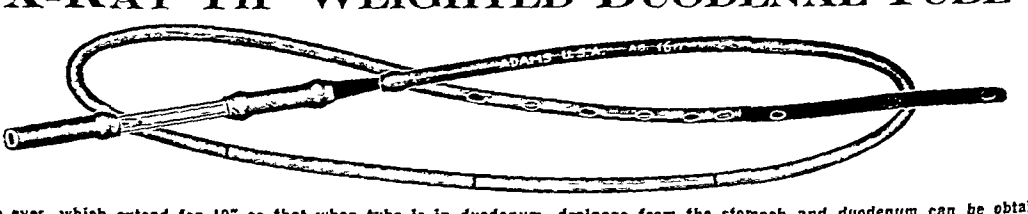
J. Duffy Hancock, Louisville.

GAY, L. P.

"Gastro-Intestinal Allergy: The Duodenal Ulcer Syndrome." South. Med. Journ., 28:1153-1156, Dec. 1935.

Some cases presenting typical duodenal ulcer symptoms can not have the presence of the ulcer confirmed by the usual clinical methods or operation. Other cases, where the ulcer is demonstrable, resist the usual medical or surgical treatment. The interesting suggestion is made that the cause in at least some of these cases may be a gastrointestinal food allergy. A series of 33 cases presenting allergic symptoms is given. In this group good clinical results, evidenced by relief from sensation of pressure, hunger, pain, and hemorrhage, were obtained in 70 per cent of the patients following the proper restriction of diet. Instances are noted where the symptoms could be repro-

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duced by the inclusion of the offending foods in the diet.

All duodenal ulcer patients are quizzed as to major and minor allergies of their antecedents and progeny as well as of themselves. Those presenting some type of allergic history are subjected to cutaneous tests which are read 24 hours as well as 20 minutes after injection. Because of the inadequacy of these findings, a trial diet and carefully kept food diary are also essential to the diagnosis. Fortunately, it is unusual to find more than 3 or 4 foods that actually reproduce the clinical symptoms. Wheat was the most common offender, and interestingly enough was closely followed in order by milk, potatoes, and rice, usually employed in the conventional ulcer diet.

The possible etiological significance of allergy in relation to duodenal ulcers may be supported by the following hypotheses: first, the mere muscular action of digestion may rub protein to which the patient is sensitive into the gastric or duodenal mucosa causing localized anaphylaxis and ulcer formation, secondly, the usual hyperirritability of the average allergic predisposes to pyloroplasm and gastric retention both of which are apparent contributing causes to ulcer formation and persistence, thirdly, the cyclic seasonal variation in ulcer symptoms may be due to the seasonal variation of foods ingested, and lastly, the pain of ulcers may be explained by localized anaphylactic spasm since focal reactions have been observed following the intradermal injection of test solutions.

The suggestions advanced seem worthy of very thoughtful consideration.

J. Duffy Hancock, Louisville.

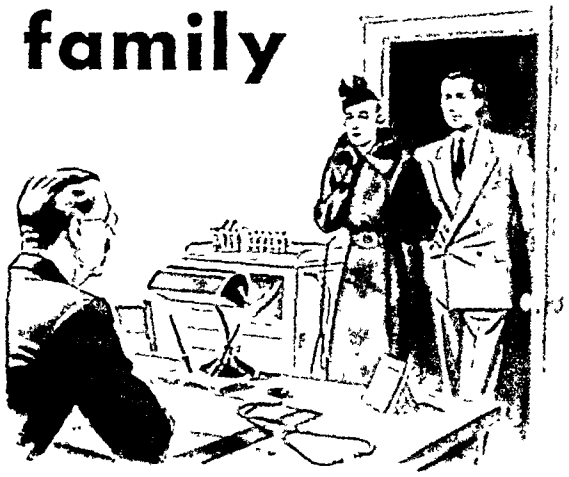
SCHMEISSER, HARRY C.

"Phytobezoar Diospyri Virginianae—Report of Two Cases." South. Med. Journ., 28:987-990, Nov., 1935.

Foreign bodies found in the stomach and intestines are of two kins: the preformed such as nails, hairpins, etc., and those formed after such substances as hair, food, etc. are swallowed. The general name "bezoar" is applied to this latter group. Bezoars may be subdivided into four groups: the trichobezoar or hair ball, the phytobezoar or food ball, the trichophytobezoar composed of hair and food (really a form of trichobezoar), and the shellac-bezoar which results when an alcoholic solution of shellac is precipitated in the stomach.

The two cases reported belong to the phytobezoar class since each was the result of the ingestion of a large number of persimmons. Thirty other authentic cases had been previously reported in the American literature. The two cases are described in detail and X-ray photographs are included in the article. Each patient had eaten approximately a quart of persimmons, there had been

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immediate nausea and discomfort or mild pain in the epigastrium, and within a very short time a mass appeared which was persistent. In one case the food ball was single and in the other multiple. Each case was treated surgically and followed by an uneventful convalesence after the removal of the mass through an opening in the stomach. Ulceration of the gastric mucosa was noted in one case.

J. Duffy Hancock, Louisville.

FREEMAN, E. B.

"A Discussion of the Essential Procedures Employed in the Diagnosis of Diseases of the Esophagus." South. Med. Journ., 28:981-986, Nov. 1935.

Possibilities for the operative treatment of diseases of the esophagus have been increased by the recent advances in thoracic surgery. For this and other reasons more attention should be given to the diagnosis of those lesions. A consideration of the usual symptoms of dysphagia pain and regurgitation is not enough. In addition, roentgen ray examination, esophagoscopy and the passage of esophageal bougies are special procedures which should be utilized in most cases. The diseases may be considered under one of these groups: malignancy, chronic cardiospasm, cicatricial stenosis, diverticulum, foreign body obstruction, hysteria, and the rarer lesions such as polypus, peptic ulcer of the lower end of the esophagus, and congenital shortening of the esophagus.

In *malignancy*, the dysphagia comes on slowly, progressively becomes worse, involves at first only solid food and then later liquids. Regurgitation appears early and is quite troublesome but the quantity regurgitated is never large. Pain is a late symptom and seldom severe. X-ray examination shows an irregular, moth-eaten filling defect. Esophagoscopy not only affords visualization but may offer an opportunity for a biopsy. The passage of a carefully guided bougie will show a more narrow caliber obstruction than is seen in cardiospasm.

In *cardiospasm*, the dysphagia comes on suddenly in attacks between which there are long intervals of complete relief. Regurgitation appears early in the disease and the amount of food regurgitated becomes increasingly large. Severe pain is unusual but there is frequently fullness or pressure beneath the lower end of the sternum. Roentgen ray examination will show a large dilated esophagus smooth in contour and tapering to a point at the cardia. Esophagoscopy will confirm the possibility of a concurrent malignancy. The advantage of the use of a guided bougie has been mentioned.

The *dysphagia of cicatricial stenosis* is rather characteristic. The acute inflammatory reaction following swallowing of caustic fluids causes an immediate difficulty in swallowing. This subsides only to be followed later after cicatrization occurs, by dysphagia which may be quite serious. Regurgitation is not a prominent symptom. Neither is pain after the first irritation. X-rays show a definite obstructive area, with moderate dilatation above. Esophagoscopy is not of nearly so much importance. Bougies will aid in determining not only the extent but the number of strictures.

In *diverticulum* the dysphagia comes on slowly and is often accompanied by a swelling in the side of the neck. Regurgitation never occurs in the same degree as in chronic cardiospasm. Pain is neither severe nor characteristic. It is more likely to occur in the traction type and be referred to the mid-sternal or lower-sternal region. X-ray examination will demonstrate the pouch. Esophagoscopy is not of great value.

Foreign bodies cause immediate difficuly in swallowing and any attempt to do so causes pain. Otherwise the pain depends upon the amount of inflammatory change. Regurgitation is not a prominent symptom. Roentgen ray examination is of value not only in cases of opaque bodies but also in those of non-opaque bodies since the oral administration of an opaque mixture will contrast their shadow. Esophagoscopy is of great aid in treatment as well as in diagnosis.

The *dysphagia due to hysteria* depends upon the nervous state of the patient, rather than the character of food ingested.

Congenital shortening of the esophagus may cause quite severe pain. It is usually paroxysmal and may be accompanied by symptoms of mild collapse. Dysphagia may be present particularly if a large portion of the stomach is above the diaphragm.

Benign polyps and *ulcers* may be symptomless and the diagnosis depend entirely on esophagoscopy.

Esophagoscopy is emphasized as a procedure neither superfluous nor dangerous. It can be done in a well equipped office or out-patient clinic. Hospitalization is not necessary and the information obtained is frequently of great value.

J. Duffy Hancock, Louisville.

LOBEY, F. H. AND SWINTON, N. W.

"Gastrojejunal Ulcer and Gastrojejunocolic Fistula. S. G. O., Vol. 61; No. 5, Nov. 1935, pp. 599-612.

In a review of the literature the authors found a great range in the reported incidence of gastrojejunal ulcer following gastro-enterostomy (from 1.7 per cent to 24 per cent). Following gastric resection the reported incidence varied from 0.4 per cent to 10 per cent. It is generally believed that the true incidence of gastrojejunal ulcer and gastrojejuno-colic fistula is higher than is reported. Males are more frequently affected than females.

The ulcer is usually found either in the stoma of the anastomosis or in the posterior wall of the jejunum opposite the stoma. Numerous theories have been proposed to explain the development of these ulcers. The theory of the ulcer diathesis doubtless explains the recurrence of ulcer in certain types. Infection in one situation or another (teeth, tonsils, appendix and gall bladder) has been shown to be an important factor in the development of ulcer. In a series of 36 cases Hurst found only two who did not have tooth infection. Unquestionably hyperacidity plays a prominent role in the etiology of gastrojejunal ulcer. Various authors report hyperacidity in from 75 to 95 per cent of their cases of gastrojejunal ulcer. It does not appear that the use of non-absorbable suture materials, or the use of clamps, or high placement of the anastomosis are factors of importance in the development of these ulcers. Willis states that the "silk or linen suture is simply a bystander and not the cause of the lesion".

Certain features of the symptoms of gastrojejunal ulcer are characteristic. After a period immediately after operation during which the individual is entirely free from symptoms, there is a recurrence of ulcer symptoms of greater intensity. The pain is less regularly associated with meals and is much less responsive to treatment. Hemorrhage and melena, in the opinion of the authors, is much more common. The point of tenderness in the abdomen is more toward the left and above the umbilicus. The diagnosis is established by X-ray examination.

There is probably no effective prophylaxis against the development of gastrojejunal ulcer. The patient must understand that careful regulation of his habits as regards eating, drinking and smoking must be maintained perhaps more rigidly after operation than before. It is generally believed now that exclusion of the alkaline duodenal contents from the stomach, (as by closure of the pylorus during gastroenterostomy) predisposes to the development of gastrojejunal ulcer. Theoretically anterior gastroenterostomy should be complicated by a greater number of gastrojejunal ulcer than posterior gastroenterostomy because the site of anastomosis is farther from the duodenum, and therefore less resistant to the acid gastric contents. The senior author feels that anterior gastroenterostomy is preferable because such an anastomosis is farther removed from the transverse colon and for that reason is less apt to be the site of gastrojejuno-colic fistula. The technical difficulties of the surgical treatment of gastrojejuno-colic fistula associated with posterior gastroenterostomy justify that feeling. This complication is said to occur in about 11 per cent of the cases. The presence of gastrojejuno-colic fistula should be sus-

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pected when a patient with gastrojejunal ulcer shows lienteric diarrhoea and loses weight even though their food intake is adequate. The diagnosis of large fistulas can be readily made by X-ray examination.

There is a distinct conviction on the part of most persons dealing with ulcer that patients with gastrojejunal ulcers seldom respond satisfactorily and permanently to medical treatment, but that in all cases medical treatment should be carried out to reduce the acidity and possibly also the area of inflammation reaction about the ulcer, thereby improving the patient's condition as an operative risk.

The surgical treatment of gastrojejunal ulcer may be simply unhooking the gastroenterostomy and re-establishment of the continuity of the intestinal tract (which is followed by a high percentage of recurrences of the primary ulcer), or it may be radical subtotal gastrectomy which is followed by a mortality disturbing to the patient and surgeon.

Small gastrojejuno-colic fistulas may be handled satisfactorily. Large fistulas present almost insurmountable problems. Block resection of the inflammatory mass and anastomosis of the free ends of bowel is a procedure of such magnitude as but very few patients can withstand. Resection of the stomach proximal to the site of the ulcer and re-anastomosis with the jejunum lower down (a sort of exclusion operation) has been performed successfully by the authors on two occasions.

Seven figures and a large bibliography accompany the article.

Nelson M. Percy, Chicago.

EXPERIMENTAL PHYSIOLOGY

BEST, RUSSEL R., AND HICKEN, N. FREDERICK.
Biliary Dyssynergia: Physiological Obstruction of the Common Bile Duct. S. G. O., Vol. 61, No. 6, Dec. 1935.

Dilatation of the bile ducts and intrahepatic biliary radicals indicates an obstruction to the free flow of bile from the liver to the duodenum. Calculi, inflammatory reactions, strictures, neoplasms, kinks, and functional derangements of the choledocho-duodenal-sphincteric mechanism are the most important obstructive agents. Considerable attention has always been placed on the organic obstructions of the common duct, but little attention has been paid to the physiological dysfunctions of the choledochal sphincter which are capable of producing an enormous dilitation of the entire bilinry tract.

The authors present case reports and experimental investigations which indicate that a hypertonicity or "dyssynergia" of the choledochal sphincter may mechanically interfere with the evacuation of the gall bladder and bile ducts,

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thus producing a stasis of bile with a dilitation of the biliary radicals. Such a sphincterismus was demonstrated in four patients by direct roentgenographic visualization of the bile ducts following the introduction of lipoiodine. In one instance spastic contraction of the common duct sphincter persisted for three hours before it relaxed and permitted the lipoiodine to enter the duodenum.

Cases are presented showing that the hypertonicity of the common duct sphincter may be independent of, or associated with, a generralized infection of the biliary tract, the presence of stones, strictures, kinks or pancreatitis. The extirpation of the gall bladder, the removal of the stones, the division of the stricture and the drainage of the infected bile ducts do not always overcome the spasticity of the sphincter, for in some cases it persisted after these operative measures.

In many of these cases possessing a spastic dysfunction of the choledochal sphincter, a cholecystectomy would not necessarily be curative, for following the removal of the gall bladder, the intrinsic spasm of the common bile duct sphincter may continue. Four patients having a spasticity of this sphincter were studied by the authors by lipoiodine visualization for as long as 33 days following a cholecystectomy and the sphincterismus still persisted. This often accounts for the "hepatic neuralgia" and persistence of gall bladder distress following surgery.

Relief of these persistent symptoms depends on obtaining a relaxation of the spastic sphincter. Westphal has demonstrated that it is innervated by the autonomic nervous system and hence the hypertonicity can be relieved by atrophine. Intraduodenal instillations of magnesium sulphate or olive oil have also been used with beneficial results in these cases.

Charles T. Sturgeon, Los Angeles.

UNGAR, G.; CONTIADES, X. J., AND PALMER, R. G.

Libération de Substances Histaminiques par Excitation du bout Péripherique du nerf Splanchnique. C. rend. Soc. Biol., Paris, 120, 328-330. 1935.

Stimulation of the left splanchnic nerve of dog A produced an increased secretion of gastric juice from dog B (to which dog A had been anastomosed by the jugular veins and carotid arteries). This secretion from dog B occurred about eight minutes after the splanchnic nerves of dog A were stimulated. After several hours of such stimulation dog A showed haemorrhagic intestinal lesions. Injection of histamine into the artery supplying an isolated intestinal loop produced, after several hours, haemorrhagic lesions of the intestine similar to those produced by splanchnic nerve stimulation. Therefore the authors conclude that a histamine-like substance is liberated at the terminal nerve-endings of the splanchnic nerve.

M. H. F. Friedman, Montreal.

PASTEUR, VALLERY-RADOT.

"Urticaria." (A special number entirely devoted to the question in the review: "Nutrition", Paris, Tome 5, No. 1, 1935).

This is an almost complete review of our actual conceptions on allergy, following the works of Widal, Abrami, Joltrain and the author, whose authority is well known.

Urticaria is composed of a humoral trouble with vascular and haematologic perturbations in an individual already sensitized to an heterogeneous albumin. American and German Schools, in their research on skin reactions produced by an antigen, have confirmed the allergic nature of urticaria. Later, the authors have noticed that the crisis was launched not only by heterogeneous albumin, but also by a cristalloid or a physical agent, such as cold, in non-sensitized persons, although taking part in the colloidoclasic diathesis.

The Author *actually* recognizes four principal groups or classes of urticaria: 1. The *urticaria of anaphylactic* origin, as shown by skin tests; 2. The *urticaria or colloidoclasic origin* with no obvious urticaria; 3. *Urticaria due to various humoral troubles of sympathetic origin*, subsequent to an acido-basic imbalance of the serum by glandular insufficiency or by chemical deficiency of the digestive tract; 4. *Urticaria following an exaggeration of the normal vaso-motor phenomenon* in cases of vago-sympathetic dystonies, so that urticaria is not due to a univocal pathogenesis, the splanchnic system being liable to receive a stimulation from various humoral causes.

Each of these types is studied at length.

1. Urticaria due to an imbalance of the vago-sympathetic system. This urticaria is produced without anaphylaxis and is oftener met amongst females. It is revealed by the following symptoms: headache, Quincke's oedema, anguish, palpitations, fatique, emotivity, cryesthesia, erythematous patches on the skin, instability of the central temperature and of the pulse, arterial hypotension, sometimes thyrotoxicosis, increase in the basal metabolism, ovarian dysfunction. In these patients, the least incident will launch urticaria: emotion, meals, heat, cold, etc.

The treatment consists of an appropriate diet, intramuscular injections of a calcium soluble salt, repeated small doses of gardenal, belladonna, scopolamine, eserin, pilocarpin. The functions of the thyroid gland must be well investigated into as also those of the ovaries. These patients should be directed to take brisk walks or light efforts twice a day; hands should be ducked several times a day in cold water, if cold is the cause, and a tepid bath should be followed by a cold sponge bath. It is possible that these tests will show a reappearance of the phenomenon but after some time the crisis will decrease and disappear. One must admit this treatment is rather vague.

2. *Urticaria of digestive origin.* It is one which appears in an individual with a predisposition, following the ingestion of a special food without any previous digestive troubles. The rash is characterized by patches, some well circled, round or irregular, isolated or confluent, pink or red, localized or generalized, with dermographia in the neighboring territory, whereas edema is found on the mucosae, especially in the mouth. Pruritis precedes or follows eruption. Patches appear and disappear rapidly, but are identified by papules, vesicles or marked edema in the territories where the connective tissue is looser, such as the face, eyelids, lips. It lasts a few hours; the progress is rapid, but it may manifest in several attacks.

This state, sometimes accidental and unique, in other cases will show remittent or permanent. This eruption is accompanied by an acute gastro-intestinal state, often febrile, of the type of an acute gastritis with fever: coated tongue, nausea, vomiting, diarrhea, enteralgia, fever, sometimes preceding the eruption. These accidents will eventually occur in already dyspeptic individuals or long standing hepatic patients, etc.

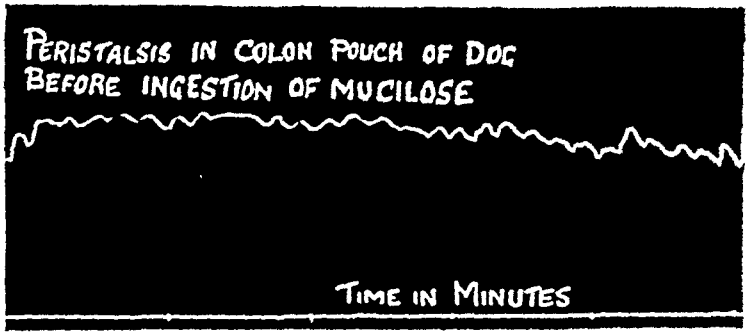
This study of the gastro-intestinal urticaria is persued and divided into several stages:

1. *The alimentary phase*, caused by a determined food, the existence of which is proved in introducing intradermically a small quantity of it after sacrification.

2. *The digestive phase*, recognizable by an acute gastro-intestinal condition. At this stage, food is not always the direct cause, but may be the cause initiating the accidents following previous attacks. Pyorrhea is frequently held responsible for some of those conditions, and this opinion should be compared with the ancient one which explained the rash of the infants by the eruption of the first teeth. In such cases an *ad hoc* treatment aiming at the digestive condition should be reached: diet, digestive stimulants, intestinal desinfection, thermal cure.

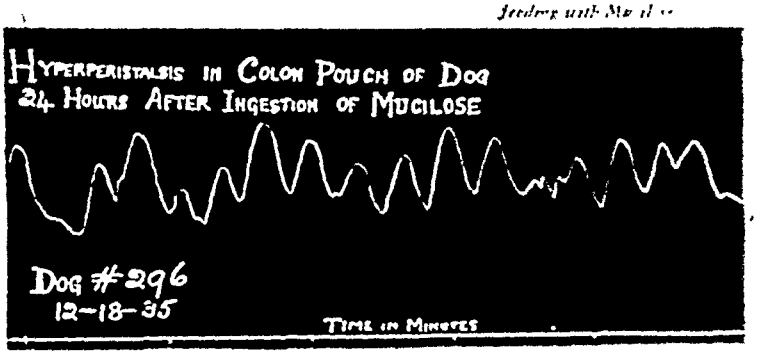
3. *The hepatic phase.* The proteopexic and the proteolytic stage of the liver is apt to intervene in the mechanism of urticaria. Disturbances of the proteolytic function favor the formation of proteins which might produce urticaria and the troubles of the proteopexic function are liable to stop the

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hepatic "barrier" opposed to the proteins absorbed from the bowels. The hemoclastic "shocks" due to an ingestion of milk well demonstrate this.

4. *The blood phase.* The essential phenomenon is produced in the blood: Arterial hypotension, leucopenia with inversion of leucocytosis, decrease in the number of the hematoblasts, the fall of the refractometric index, the blood hypercoagubility, are well in evidence. Shock is also tissular. This sudden sensitization of an individual to a food which he has ingested all his life with no accident suggests the idea of an idiosyncrasy but the process is the same.

5. *The skin or neuro-vegetative phase.* The vaso-motor trouble, *i.e.* eruption and pruritis, must be considered as symptoms of a nervous stimulation: one, the vaso-motor troubles, of neuro-vegetative origin, and the second, pruritis, due to a sensitization of the nerves, a consequence of the former.

One must bear in mind, in those cases, the *role* of the endocrine glands, but this neuro-vegetative sensitization will oftener result from a deficient condition of the digestive tract or of the liver.

In conclusion, in the presence of a case of urticaria, it is most important, according to the Author, that the condition of the digestive tract and of the liver be investigated: "and this must be accepted as a merely theorical conception, as experience shows that, in several cases, it is the only way of improving or curing a state of allergy".

Jean Le Sage, Montreal.

UNGAR, G.; CONTIADES, X. J., AND PALMER, R. G.

Libération de Substances Histaminiques dans les Infarctus de L'intestin. C. rend. Soc. Biol., Paris, 120, pp. 326-328, 1935.

Embolisms are produced by injecting aqueous powder suspensions into a branch of the mesenteric artery. Six to ten minutes later there is a great increase in the gastric secretion. To eliminate all nervous activity, carotid-jugular cross-circulation experiments were carried out. All this was thought to show that a histamine-like substance is liberated in the course of intestinal embolism.

M. H. F. Friedman, Montreal.

THERAPEUTICS

HURST, ARTHUR F.

Ulcerative Colitis, Guy's Hospital Reports. Vol. 85, No. 3, pp. 317-355, July, 1935.

Hurst emphasizes the difficulty of distinguishing ulcerative colitis from bacillary dysentery by the use of the sigmoidoscope. Many instances in the past and present of finding *B. dysenteriae* in the stools and ulcer-bases of cases of ulcerative colitis are recorded, and Hurst frankly feels that *B. dysenteriae* as a group is the fundamental etiological factor in the disease.

Upon this may be built, from time to time, recurrences due to re-infection by other microorganisms,—*B. coli* and *enterococci* which have acquired enhanced virulence; parenteric organisms swallowed in the food; *streptococci* swallowed during acute tonsillitis.

Distinction from amoebic dysentery can usually best be made by the therapeutic test with emetine. Other confusing diseases are hemorrhagic proctitis, carcinoma of the pelvic colon and rectum, polypi, purpura, multiple telongiectasis, enteritis. "Regional" ulcerative colitis as, for example, of the sigmoid, may be recognized chiefly by the roentgen appearances.

The usually mentioned complications are dealt with at length. If achlorhydria be present, and lavage with hydrogen peroxide does not cause acid secre-

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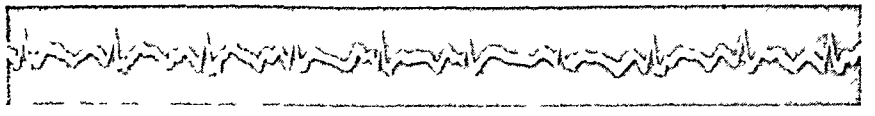
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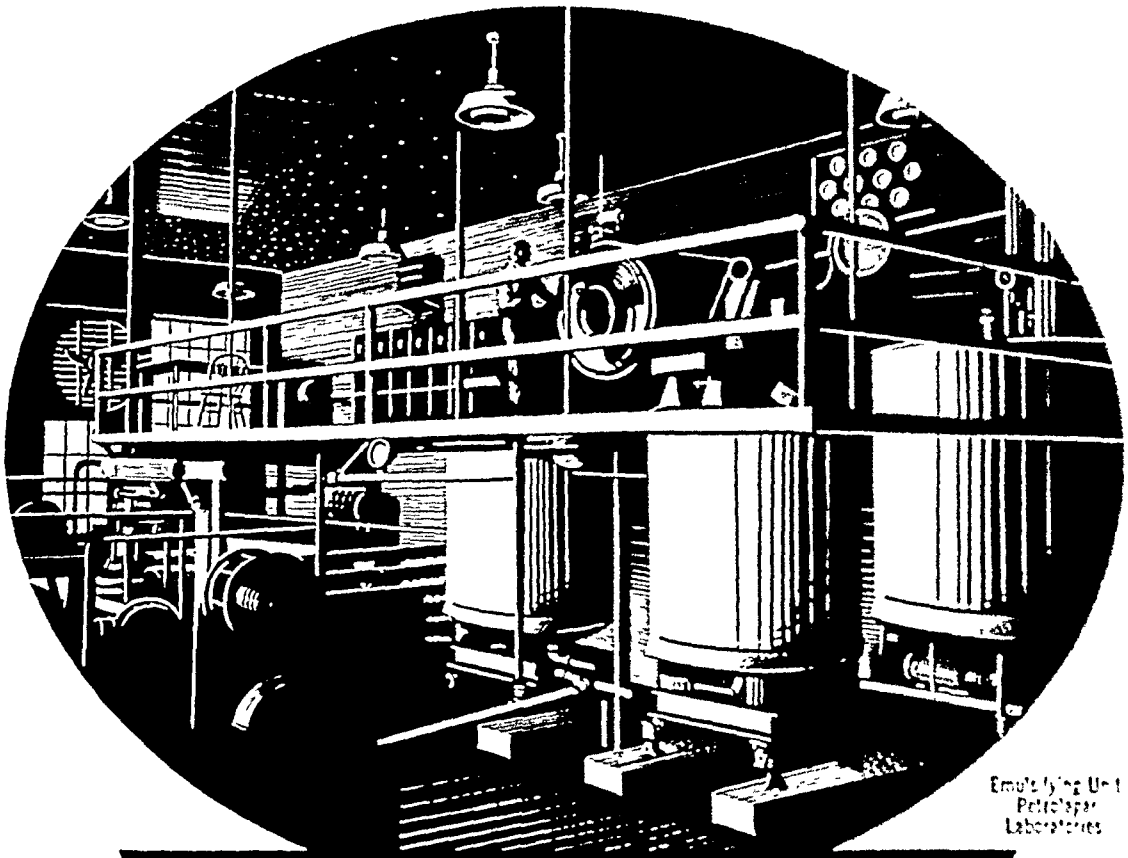
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tion to re-appear, he then gives the patient HCl for the balance of his life.

Prospects of recovery appear good to the author provided patient and physician cooperate thoroughly and treatment be continued long enough.

The use of anti-dysenteric serum intravenously is the treatment which Hurst himself began 15 years ago, and from which best results are obtained. (Corroborative evidence of the efficacy of this form of therapy was presented in the August, 1935, issue of this Journal). This should be given as early in the disease as possible. Rest, a low-roughage diet, soothing enemas, codeine, belladonna, charcoal, iron, blood transfusions (when needed) are other phases of the medical methods which Hurst employs.

Caecostomy or appendicostomy frequently assists recovery in stubborn cases, but is reserved for those in which the whole colon is involved and in which improvement has failed to follow medical treatment. Colectomy and short-circuiting are usually to be condemned but occasionally, in spite of the hazards involved, a strikingly good result may be obtained. Dilatation of rectal strictures is safely accomplished by means of a finger-stall which is placed in situ and cautiously inflated with air until slight pain is produced. Hurst does not regard Bargen's organism as being the cause of the disease.

Beaumont S. Cornell.

ABDOMINAL SURGERY

BUCKBINDER, J. R.

Surgical Limitations in the Treatment of Acute Suppurative Peritonitis. S. G. and O., Vol. LIX, No. 3, pp. 485-490, Sept., 1934.

The Author proposes to indicate what appear to be certain basic errors in the clinical appraisal and pathological diagnosis of acute peritonitis in the light of experimental and clinical observation, and to suggest what surgical limitations are imposed in the management of this disease. It has been shown that two functions of the peritoneum are of major importance; absorption and exudation. Absorption occurs in all parts of the peritoneum. It is retarded by albuminous solutions, by hypertonic solutions, by cold, by distension, by fibrin, and other substances. Exudation is the typical peritoneal response to inflammation. That exudation, which is normally serious, rapidly shows fibrin in the presence of irritation. Moderate inflammation provokes the formation of an abundance of fibrin, while a virulent infection may not produce any fibrin. It has been shown that no substance, however bland, can be introduced into the peritoneal cavity without causing the formation of fibrin. Steinberg concluded, from an experimental study, that the cause of death in diffuse peritonitis was the bacterial toxins; that intestinal paralysis, stasis, and bacteria play no part.

That there is frequently a basic error in the clinical diagnosis and the pathological diagnosis, especially in cases of acute spreading and acute diffuse peritonitis, is evident from a study of the clinical reports on cures of so-called "general" peritonitis. The clinical signs of spreading peritonitis will not usually tell its full extent; at operation one is not justified in determining the extent of the infection by exploring uninvolved portions of the abdomen. The lessened toxic reaction that accompanies fibrin immobilization, the usual absence of ileus, and a sharply demarcated zone of tenderness are differentiating features. Ileus, thready pulse, and vomiting are associated with a diffuse process. The Author considers the term "general peritonitis" a misnomer, and considers that in most instances it should be restricted to patients who are moribund.

In considering the problems involved in peritoneal drainage, the point that is frequently lost sight of is the difference in the reaction to drains of the diffuse

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and localized types of infection. Drainage of diffuse peritonitis is always inadequate. Peritoneal abscess always requires drainage. Drainage can definitely be omitted when one is dealing with an unquestionably diffuse process. The Author believes that areas of definite encapsulation should be drained since they usually precede pus formation. Unencapsulated areas of pus are too often drained. A common example of such an error is the case of phlegmonous appendicitis in which unencapsulated pus has gone into the pelvis, or in which a spreading infection accompanies the appendicitis. It was for such a condition that surgeons a generation ago made multiple incisions, and put rubber tubes, or gauze, into each one. The Author has shown that drains in such cases are encapsulated within a remarkably short period of time, and subsequently do more harm than good. Experimentally the damage most uniformly evoked by such drainage is residual abscess, which abscess is less likely to disappear than such an abscess as forms in the absence of drains.

It would seem that the surgical treatment of spreading peritonitis is limited to the removal or closure of a septic focus, aspiration of the exudate, and closure of the peritoneum without drainage. The abdominal wound above the serosa must be drained. Both the experimental and clinical observations of the Author are opposed to the opinion that operation during a spreading peritonitis increases the rate of spread of the infection. Post-operative spreading peritonitis as indicated by distention of the abdomen, nausea, and vomiting, with mounting temperature and persistently high pulse should be treated by re-opening the abdomen rather than by waiting. Post-operative abscess should not be attacked until it is of sufficient size to assure both complete walling off, and indications of its location. In such instances the shortest route to the infection should be followed; fresh fibrin adhesions should be regarded as inviolate. A pelvic gravitation abscess impinging upon the rectum can be drained more readily through the rectum than along the old drainage tract.

N. M. Percy, Chicago.

WARREN, S., AND EBERHARD, T. P.

Mesenteric Venous Thrombosis. S. G. and O., Vol. 61, No. 1, pp. 102-121, July, 1935.

The authors review 73 cases of intestinal obstruction due to thrombosis of the mesenteric veins, and present two new cases.

In most cases no adequate cause for the thrombosis can be discovered. There are several predisposing factors the existence of which, along with symptoms of acute, or sub-acute, obscure abdominal distress, should suggest the diagnosis. Those causes may be grouped roughly into four major groups: Infections, hematogenous, traumatic and mechanical.

Pain which may be generalized or localized to one part of the abdomen is usually the presenting symptom. The character of the pain is not distinctive. Vomiting occurs early as a reflex phenomenon, and later as a result of obstruction. The vomitus may be bloody, like "coffee grounds" or fecal depending on the site of the thrombosis and its duration. Neither constipation nor diarrhea is characteristic of the condition. Some distention and a degree of shock soon develop. The pulse will be elevated, weak and frequently irregular. The temperature will be subnormal early. Marked leukocytosis averaging from 15,000 to 30,000 is one of the outstanding features of the disease.

All writers agree that melena is a diagnostic point in differentiating those obstructions with impairment of circulation and those without it. More general use of the diagnostic enema

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Carefully checked clinical and hospital records show that constipation is an ever present threat that must be seriously considered in all cases of gastric ulcer.

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would increase the percentage of correct diagnoses in this condition.

If the disease is diagnosed early and surgical treatment instituted, there is hope of recovery. The prognosis is very poor if the condition is treated expectantly; after 24 hours of acute symptoms the prognosis is extremely bad. The consensus of opinion today seems to be that the infarcted bowel and its obstructed blood supply should be removed. It makes little difference whether anastomosis is undertaken at that time. Several authors have emphasized the importance of resecting the bowel far into healthy tissue. If anastomosis is to be undertaken at the time of the primary operation, it is all important to have healthy bowel for the procedure; any bowel with incipient thrombosis should be excised.

Eight tables and a large bibliography accompany the article.

N. M. Percy, Chicago.

ROLLER, C. S.

Mesenteric Cysts. S. G. and O., Vol. 60, No. 6, pp. 1128-1136, June, 1935.

Mesenteric cyst is possibly the rarest tumor in the abdomen. It occurs at all ages of life and along any mesentery. They seem to occur twice as often in females as in males.

It seems impossible to determine accurately the etiology of these cysts. The author presents a classification as follows: (1) Embryonic inclusion tumors, (2) chylous cysts, (3) bacterial or parasitic cysts, (4) traumatic cysts, (5) angiomata of blood or lymph vessels, and (6) gas cysts.

These tumors are usually symptomless but may give rise to symptoms of partial intestinal obstruction, or symptoms referable to whatever organ it may be pressing upon. Some authors have observed the tumors are more freely movable laterally than they are vertically.

The treatment of mesenteric cysts is purely surgical. Enucleation of the cyst without disturbing the bowel or its blood supply is the safest and most satisfactory method. Resection of the bowel and mesentery, or marsupialization of the cyst may be necessary.

The mortality varies from 10 to 50 per cent, but has been stated by Atchley to be 35 per cent for all cases.

The author reports 3 cases in detail.

Seven figures and a large bibliography accompany the article.

N. M. Percy, Chicago.

SEELY, H., AND ZOLLINGER, R.

Fundusectomy in the Treatment of Peptic Ulcer. An Experimental Study. S. G. and O., Vol. 61, No. 2, pp. 155-161, Aug., 1935.

The Authors performed experiments designed to determine whether fundusectomy performed in normal dogs of nondescript breed would permanently reduce the amount of free or total acid in the stomach. The fundus was excised from four dogs leaving a tube of stomach extending from the esophagus to a point within six centimeters of the pylorus. This tube was made up chiefly of the magenstrasse, was smooth and free of rugae. Postoperatively there was to be a marked drop in the amount of free and combined acid which, however, steadily rose until it reached the normal preoperative level after about eight months. At necropsy the stomachs were fixed in distended state and studied microscopically. Grossly they had the size and shape of a normal stomach, but contained no rugae. Microscopically they showed a rich distribution of acid bearing cells especially along the greater curvature.

From their studies the Authors conclude that fundusectomy has little to offer as a means of permanently reducing gastric acidity.

Nine figures, a brief review of the literature, and a bibliography accompany the article.

N. M. Percy, Chicago.

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IN all forms of dyspepsia other than those arising from gastric ulcer or cancer, Vichy Celestins is of distinct service. Being easily assimilated, the water promotes gastric secretion and tends to normalize the function of the gastric glandular apparatus. In gastric neuroses and the milder forms of organic disease of the stomach, the stomach is soon physiologically improved, digestion accelerated, fermentation neutralized, and pain and nausea alleviated.

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CANNED FOODS AND THE PUBLIC HEALTH

III. Chemical Preservatives

• Some of our readers have inquired as to whether or not chemical preservatives are used in commercially canned foods. In certain instances, this question was inspired by the fact that "canning compounds" were formerly sold for use in home canning and preserving operations. Such compounds, however, are rarely used by the housewife of today, and never by commercial canners.

We wish to state here that *no preservatives are used in commercially canned foods.*

Spoilage of food is principally caused by the growth and multiplication in food of microorganisms such as yeasts, molds, or certain types of bacteria. These microorganisms depend upon the food they inhabit for their nutrition and their life processes produce changes in the chemical or physical characteristics of food, or both. These changes lead us to state that the food has "spoiled".

Like other living organisms, these spoilage microorganisms can grow and multiply in a food only as long as conditions remain favorable for their existence. If any environmental factor, such as temperature, moisture or acidity, becomes unfavorable, these spoilage organisms are destroyed, or their development is inhibited.

All methods of food preservation have a common underlying principle; they all alter some factor or factors in the food environment so as to render conditions unfavorable for the growth or development of spoilage organisms in the food.

Thus, foods may be preserved by freezing or refrigeration, which serves to lower the temperature below that optimum for growth of certain spoilage organisms; dried foods keep because the moisture content has been reduced to an unfavorable low level; certain fermented foods keep because of the development of high acidity. All of these methods produce changes in the environment in which the food spoilage organisms must live.

Commercial canning is a method of food preservation in which the temperature factor in the environment is raised to a level above that optimum for growth of spoilage microorganisms. Thus, canned foods keep because in their preparation they are subjected to heat processes in hermetically sealed containers. The thermal processes raise the temperature of the foods to those temperatures at which the most resistant spoilage organisms present cannot grow or survive. (1)

The hermetic seal insures protection against future infection of the food by such organisms.

Thus, commercial canning is a method of food preservation which has for its basis the thermal destruction of spoilage organisms; no chemical preservatives are needed to insure preservation of the foods, and, consequently, none are used

AMERICAN CAN COMPANY

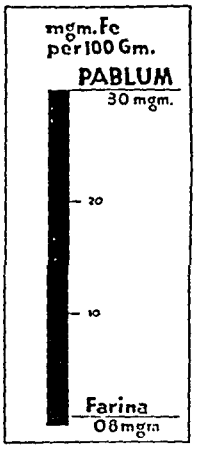
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This is the eleventh in a series of monthly articles, which will summarize, for your convenience, the conclusions about canned foods which authorities in nutritional research have reached. We want to make this series valuable to you, and so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles.

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FAR too often the bland diet prescribed for gastric ulcer, colitis, and similar gastro-intestinal disorders is a deficient diet. An analysis made by Troutt of ulcer diets used by 6 leading hospitals in different sections of the country showed them to be "well below the Sherman standard of 15 milligrams" in iron and low in the water-soluble vitamins.[1] "Vitamin B would appear to be represented at a maintenance level in most cases," writes Troutt, "but the possible relation of vitamin B to gastro-intestinal function and appetite should make one pause before accepting a low standard."



Although Pablum has a low fiber content it is 37 times richer than farina in iron and in calcium, 4 times richer in phosphorus, and 4½ times richer in copper.

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Pablum is the only food rich in a wide variety of the accessory food factors that can be fed over long periods of time without danger of gastro-intestinal irritation. Its fiber content is only 0.9%. Yet Pablum contains 37 times more iron than farina and is an excellent source (+ + +) of vitamins B and G, in which farina is deficient. Supplying 8½ mgms. iron per ounce, Pablum is 8 times richer than spinach in iron.

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The high vitamin B content of Pablum assumes new importance in light of recent laboratory studies showing that avitaminosis B predisposes to certain gastro-intestinal disorders. Apropos of this, Cowgill says, "Gastric ulcer is another disorder which can conceivably be related to vitamin B deficiency. Insofar as the treatment of this condition usually involves a *marked restriction* of diet the occurrence of at least a moderate shortage of this vitamin is by no means unlikely."[2]

Requiring no further cooking, Pablum is especially valuable during the healing stage of ulcer when the patient is back at work but still requires frequent meals. Pablum can be prepared quickly and conveniently at the office or shop simply by adding milk or cream and salt and sugar to taste. Pablum has the added advantage that it can be prepared in many varied ways—in muffins, mush, puddings, junket, etc. Further, Pablum is so thoroughly cooked that its cereal-starch has been shown to be more quickly digested than that of farina, oatmeal, cornmeal, or whole wheat cooked four hours in a double boiler (studies in vitro by Ross and Burrill[3]). In addition to the above advantages, Pablum is the only base-forming cereal (except Mead's Cereal which is the uncooked form of Pablum).

Pablum (Mead's Cereal thoroughly cooked) consists of wheatmeal, oatmeal, cornmeal, wheat embryo, alfalfa, yeast, beef bone, iron salt and sodium chloride. [1-3] Bibliography on request.

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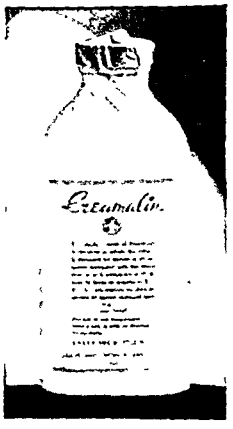
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SECTION I—*Clinical Medicine: Diseases of Digestion*

Gastroscopic Observation Concerned with the Gross Anatomy of the Stomach: The Musculus Sphincter Antri; Observation of the Position of the Stomach; The Mucosal Folds

By

RUDOLF SCHINDLER, M.D.*

CHICAGO, ILLINOIS

THE aim of this paper is to describe the interior of the stomach as seen through the gastroscope and to contrast our concept of the gross anatomy derived in this way with the older views of gastric anatomy based on anatomic or roentgenologic methods. The findings are based on over 2400 gastroscopies.

It should be remembered that gastroscopy (18) is carried out with the patient lying on his *left* side. In looking through the ocular of a gastroscope one sees a round picture which may be subdivided in left, right, upper and lower quadrants. The "left quadrant" of the visual field is *not* the left side of the stomach. For this reason the orientation is very difficult. When the expressions: "left or right, "upper or lower" are used in this paper without any supplement they refer to the quadrants of the image seen through the gastroscope and not to the stomach itself.

We shall discuss the subjects to be considered under the following three headings:

(1) Interior parts of the stomach
(2) Position of the stomach
(3) Relief of the mucosa (folds rugae).

(1) *Interior Parts of the Stomach; the musculus sphincter antri.*

The subdivision of the cavity of the stomach into a *pars digestoria* and a *pars egestoria* is generally accepted. Cunningham (5) writes: "The *incisura angularis* and the *sulcus intermedius* are distinct." He found also this subdivision in the stomach of apes. The same findings have been described in the Sirenia. Most authors agree that the descending part of the stomach to the *incisura angularis* of the roentgenologists is the digestive part; the ascending part from the *incisura angularis* to the pylorus is the *pars egestoria.*

Nevertheless, there is much confusion in the nomenclature among the anatomists and among the roentgenologists as well. The gastroscopists do not like the word *"incisura"* because seen from the inside of the stomach there is no *incisura*, but a prominence, a kind of fold, which we are accustomed to call the *"angulus"* or angle. If this point be observed from within the cavity of the body (either through the gastroscope or in a dissected stomach of the cadaver or in a phantom showing the typical angle) it may be seen that this turning of the stomach from the downward to an upward direction produces a *parabolic curve.* This curve does not interrupt the anatomical continuity of the mucosal pattern.

It seemed necessary to Plenck (14) to give a name to that part of the greater curvature which is opposite to the angle. He called it "knee of the stomach." This name, however, is not important because the "knee" is neither of anatomical nor physiological importance.

While all authors agree, that on the lesser curvature the *pars egestoria* begins at the angle, a similar demarcation has not been found on the greater curvature. The pyloric glands extend along the lesser curvature to about the angle; on the greater curvature it has not been possible to find such a sharp limitation; but in any case they do *not* extend to the "knee" (Plenck (14)).

Anatomists found various circular contractions of the pyloric part of the stomach. His (9), for instance, found a marked *incisura* between the body and the *pars pylorica;* this latter was subdivided by muscular contractions in three parts *(camera princeps, camera minor* and *camera tertia).* Early it was shown that these contractions were inconstant and were the result of peristaltic waves developing at the moment of death.

In 1907 Groedel (7) believed he had found by X-ray a *sphincter antri pylori.* This is that part of the antrum from which peristaltic waves ran toward the pylorus.

The extensive literature will be found in Franz W. Mueller's paper (13) and in Plenck's (14) monograph. The conditions as revealed by gastroscopy are not even found by the X-ray-relief method. The work and concept of Cole (4), will be discussed later. It is surprising that in the standard work of Plenck the gastroscopic conceptions have not been mentioned.

If we look through the gastroscope toward the pyloric region, using as little air as possible for the inflation, we regularly find a prominent fold, which is sometimes so high that it hinders the view of the distal parts, and which is sometimes flat. Generally it appears as a twisted rope, cordlike. It usually begins exactly at the end of the parabolic line of the angle and runs over the greater curvature and the anterior wall of the ascending branch of the stomach.

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In the posterior wall it can either be missed or only poorly observed. The cordlike appearance may be absent, in which case the fold is smooth and of the same orange-red color as the other portions of the stomach. We have often photographed this fold through the gastroscope (17) and published several colored pictures (15). In rare cases the cordlike fold is observed above the angle and may then run over the lesser curvature. Such a case has been photographed by Henning (8). I should like to emphasize that ordinarily the smooth continuation of the lesser curvature is not interrupted by a prominent fold. However, we have seen the situation in a few cases in which the clinical picture gave the impression of abnormal spasms. It may rarely occur that this fold is beyond the angle and thus lies completely in the ascending part of the stomach. The gastroscopists call this fold the *musculus sphincter antri,* and it is evident that it constitutes the true division between the two parts of the stomach. Because it never runs over the "knee" of the stomach, but much more distal to it, it is possible that the pyloric glands extend along the greater curvature to this *musculus sphincter antri.*

What is (a) the physiological significance, and (b) the anatomical substrate of this *musculus sphincter antri?*

(a) In regard to its physiology it should be pointed out that, gastroscopically, peristaltic waves are observed only (with very rare exceptions in one of five hundred examinations) in that part of the stomach which is *distal* to this fold. This part is more of a globular cavity than a tube-like canal, and for this reason we call it the "antrum pylori." The peristaltic waves never begin at the *musculus sphincter antri* except in certain pathological cases. These waves of the antrum always begin at a place distal to the *m. sphincter antri.* They are seen as circular elevations, which move to the pylorus and are accompanied by a shortening of the antrum until the closure of the pylorus is complete. This is often accompanied by the formation of radial folds which give the pylorus a stellar picture. The point of origin of these peristaltic waves varies even in the same person if one observes long enough. Generally one has to wait about one miunte until the appearance of the first contraction which is often situated near the pylorus. The succeeding contractions become more energetic and originate more proximally, but never (this should be repeated) at the *m. sphincter antri* itself. I think we have to assume that the roentgenologists have considered as their *m. sphincter antri* the place where peristaltic waves begin. It may be that the true physiological function of the *m. sphincter antri* is to act as an obstruction or valve thereby preventing the food from entering the *pars egestoria* too early.

(b) What is this fold anatomically? How is it possible to explain the cordlike aspect? This latter question can be answered easily. It is evident that the mucosa is protruded as a high fold over which the normal mucosal folds run close together, not parallel to the greater curvature, but crossing at an angle. Korbsch contended that this oblique direction is only apparent and that it is effected by an oblique visualization through the gastroscope. This is not so. We often see perpendicularly into the antrum and yet the *m. sphincter antri* still appears cordlike. On the other hand we can sometimes observe these folds parallel to the greater curvature which, however, is infrequent. The high fold itself must be formed by some muscular action because it can be flattened out by insufflation of air, can reappear, and is generally not found in the stomach of the cadaver as a persistent fold of the mucosa.

Cole (4) published a drawing of the interior of the stomach showing a definite limiting fold between body and antrum, on both the lesser curvature and the greater curvature. This roentgenologic discovery has not been appreciated enough. This fold in Cole's drawing is formed only by mucosa and submucosa without participation of the *muscularis propria.* We cannot deny the correctness of this conception, but we have reason to think that the *m. sphincter antri* is formed by the *muscularis propria ventriculi* itself. This conception as well as all our observations about size, shape and situation of the *m. sphincter antri* corresponds exactly with the anatomical findings of Stieve (20) in 1919, who is the only anatomist to have described this region as I have seen it in about 2000 examinations with the gastroscope. He examined the stomach of four executed people immediately after death and found a thick compact circular contraction in the region of the *incisura angularis.* This contraction was so firm that the finger could not be introduced into the antrum. The peritoneum was smooth. The muscularis of the antrum was one to two mm. thick, while that of the body was 0.5 to 0.8 mm. In the contracted part the muscularis was elevated to form a circular wall, 6 mm. thick, which was protruded like a tile roof into the interior of the stomach. The wall of the stomach at this point was two cm. thick. This thickened circular muscle consisted only of contracted circular muscle fibres. After opening the stomachs the antrum and the body showed a smooth surface. Only in the region of the contraction, broad, comb-like and ridgelike folds were found. These were generally parallel to the greater curvature but some were oblique. This anatomical picture corresponds so well with the gastroscopic findings that we have reason to suppose that the *m. sphincter antri* in the living man is a constant formation caused by a contraction of circular fibres of the *muscularis propria* itself.

We believe that our numerous gastroscopic observations together with the anatomical description of Stieve and the roentgenological conception of Cole should settle the question of the subdivision of the stomach once and for all.

Gastroscopically, the *nomenclature* of the parts of the stomach must then be: cardia, pylorus, anterior wall, posterior wall, lesser and greater curvature and the cavities of the "body" *(corpus)* and of the "antrum." Both cavities are separated in the region of the "angulus" by the high fold of the *musculus sphincter antri,* which is generally developed only on the anterior wall, posterior wall and greater curvature, and not on the lesser curvature. It may be practical to add the name of "fornix" for that part of the body which in upright position lies above the cardia. This nomenclature has been used by us since 1923 and has been adopted by Moutier (12).

(2) *Observations on the position of the stomach.*

The position of the stomach is seen differently by the anatomists and by the roentgenologists. There is

probably no other organ of the body, about whose gross position the opinions differ so much. The reason is the extreme mobility of the stomach, the change of its position due to various influences and different conditions under which the two methods have to be used.

(a) *The mobility of the stomach.* We often find the statement, that the stomach has two fixed points, cardia and pylorus. Gastroscopy shows us that this is wrong. The cardia or at least the diaphragmatic portion of the esophagus is certainly fixed, but not the pylorus. The pylorus generally can be well seen through the gastroscope if the patient is lying on his left side or on his knees and elbows. Moving the right shoulder forward often brings a hidden pylorus into view when using the left side position. Since the end of the rigid gastroscope always lies at the left side of the vertebral column and posteriorly, and since the end of the flexible gastroscope never leaves the posterior wall of the stomach, the pylorus appears generally in the left upper part of the gastroscopic field. This fact proves that the pylorus has left its regular position at the right side of the spine and has fallen toward the anterior abdominal wall of the patient. The short end of the duodenum between its retroperitoneal part and the pylorus is long enough and moveable to allow this important shift of the pylorus. This movement can be so extensive that the pylorus appears exactly at the left side of the observer. We have seen this in persons in whom no adhesions could be suspected. That means that the pylorus has fallen so much forward toward the abdominal wall that it is seen at the *left* side of the spine and that the cardia and pylorus are lying in a *sagittal plane.* The stomach has reached its embryologic position. In these cases, the gastroscope runs over the greater curvature or at least very close to it; this event confuses the beginner completely; he cannot imagine such an enormous mobility of the pylorus. This fact that in some cases the pylorus is found at the left side of the spine in the left side position of the patient, has been proved anatomically by Bensaude, Gregoire, and Rachet (2).

(b) *The inclination of the posterior wall.* The course of the stomach between the cardia and the pylorus is most complicated and varied. The best anatomical description has been given by Franz W. Mueller (13). According to him, the position is altered by:

(1) sex (Schlesinger), (2) position and size of liver, (3) position of diaphragm, (4) position and fullness of the intestine, (5) exterior shape of the body, (6) condition of the abdominal wall, (7) position of the body.

(1) In my gastroscopic observations I could not find any difference between the sexes.

(2) The influence of the liver cannot be determined by means of gastroscopy.

(3) A decisive influence of the diaphragm is observed as continuous shifting of the gastroscopic picture in different directions corresponding to respiratory movements.

(4) In my textbook and atlas of gastroscopy of 1923 (15) I referred to the varying fullness of the intestine due to the fact that in the different gastroscopies made in the same patient the pylorus was easily seen at one examination, but could not be found at another, although the tonus of the muscular wall of the stomach had not changed.

(5) The exterior shape of the body plays the greatest rôle in determining the position of the stomach. This will be discussed later.

(6) I have not observed any influence of the abdominal wall upon the stomach as viewed through the gastroscope. I agree in this point with the X-ray findings of Moody, van Nuys, Chamberlain (11).

(7) It has been mentioned that the position of the body is of fundamental importance for the position of the stomach. Although the French school (Bensaude, Rachet) has studied this point, the influence of the left side position has been neglected.

A plane which joins lesser and greater curvature is a warped one. In the middle of this plane between the two curvatures is the *axis* of the stomach. The plane of the axis is bent by the direction, the inclination and the rotation of the stomach. These three influences cause the plane to be warped. The inclination and rotation are little known to the roentgenologists who generally see the stomach in the anterior-posterior direction. If they would become accustomed to examine the stomach, in any case, also from the left and from the right side, they would have quite another conception of the shape of this organ. The divergence between the roentgenologic and anatomic conceptions is easily explained by the fact that the roentgenologist rarely observes the stomach in this direction and that it is impossible for him to observe the stomach in the most important transverse plane. The anatomist finds that a vertical position of the axis of the stomach never occurs, because the region of the fornix is always separated by the left liver lobe from the anterior abdominal wall while the lower pole approaches the anterior wall and often joins it. We have seen that even the pylorus often approximates the anterior wall in certain positions. The general direction of the whole stomach runs from cranial-dorsal toward caudal-ventral. In a frontal plane which is routinely used in the X-ray examinations the stomach appears shortened.

The criticism of Fr. W. Mueller (13) about the X-ray method seems to be much too harsh. He points out that the axial plane is rotated so that the greater curvature is turned toward the anterior wall and the axial plane between the two curvatures approaches the transverse plane. For this reason, the lower border of the stomach as seen with X-ray is a line of the posterior wall and not the greater curvature. This is certainly true in a great number of cases, but it should be considered that the stomach *may be stretched* by the heavy barium and then may leave its transverse position, which is so unfavorable for an X-ray examination.

The question to what degree and how often the stomach can be stretched can be settled to a certain extent by gastroscopical researches. Gastroscopy never can determine the course of the axis with certainty but often it can determine the course of the posterior wall. We choose a patient, in which the introduction of the rigid gastroscope is extremely easy, and in which it can be pushed to the lowest depth of the stomach. If we lay this patient on his back and introduce a flexible, but not elastic, metal tube and then make an X-ray exposure from the left side, we see that the tube lies at the cardia at the side of the spine and that it bends forward toward the anterior wall in a curve whose angle scarcely surpasses 30°. This ex-

periment proves that even in the most favorable position in the most apt patient the posterior wall of the stomach does not continue in the same axis as the esophagus, but that it forms an angle of about 30°. The stomach axis proper has to lie still more anteriorly, but that is not so important for the practical purpose of gastroscopy.

How often is it possible to stretch this angle and cause the posterior wall to become a straight continuation of the axis of the esophagus? This can easily be decided by recording the experiences with the rigid gastroscope. In 45 to 50% of all cases it was not possible to introduce this instrument into the lower depth of the stomach. Generally it was stopped by the posterior wall two cm. beyond the cardia. It became evident that the type of constitution played the greatest *rôle*. The 50% in which the stretching of the stomach was impossible were markedly obese, heavy people with short neck, belonging to that type of constitution which now we are accustomed to call a "pyknic" constitution. On the other hand, the remaining 50% in which the complete introduction of the rigid instrument was possible, belonged to the "asthenic" constitution. There were exceptions in both types.

The use of the flexible gastroscope permits better judgment about the size of the angle which the posterior wall forms with the axis of the esophagus. The flexible gastroscope gives a round picture only when its curve does not exceed an angle of 34°. This gastroscope is not only flexible but also extremely elastic and by its elasticity it stretches the posterior wall like a rigid gastroscope (Moutier (12)). It can, however, be introduced to the lowest depths in all those cases in which a stretching of the stomach wall is impossible. We find that in about 5% of all persons examined the picture does not become completely round, indicating that the angle between the axis of the esophagus and of the direction of the posterior wall is greater than 34° even under the stretching influence of the elastic instrument. A curious phenomenon is still seen in 2% of the other cases. If the flexible gastroscope is introduced into the lower depth of the stomach, the picture is quite round because the long elastic part has strength enough to stretch the posterior wall to an angle of 34°. If the instrument is then withdrawn and its tip is but 5 cm. beyond the cardia, the picture suddenly becomes disc shaped. This short piece of the instrument is not strong enough to prevent the stomach wall from bending it to an angle greater than 34°.

(3) *The "Relief" of the Mucosa (Folds, Rugae).*

Gastroscopy demands an inflation of the stomach by the smallest amounts of air. With this the "relief" of the mucosa can be studied excellently. It is somewhat astonishing that the results do not correspond completely with the results of the X-ray relief method.

We have tried to demonstrate, by X-ray relief-examination, marked pathological changes repeatedly seen with the gastroscope. One case was that of a rigid fold running over the posterior wall from an artificial operative opening between stomach and intestine. This fold contained numerous small rigid nodules. Another case was a man whose stomach mucosa was shown to numerous physicians in gastroscopic courses. As an end result of a very severe hypertrophic gastritis, there were two sickle-shaped, firm folds of the greater curvature, crossing it perpendicularly. The smaller one was about 6 cm., the larger one about 8 cm. beyond the cardia. We did numerous fluoroscopies and took many films in order to demonstrate these folds roentgenologically. This was impossible. We have already discussed the fact that it is generally impossible to demonstrate the true *m. sphincter antri* roentgenologically.

On the other hand, we often see on X-ray relief-pictures formations which are not observed through the gastroscope. The antrum, for instance, is gastroscopically free of mucosal folds, yet they show regularly in the relief technique films. I cannot fully understand this difference. Because I see such folds only when the patient vomits or retches, I suggest that the contraction of the *muscularis propria* causes these folds.

I have never seen any activity of these folds. This corresponds with the findings of French authors (Duval, Roux, Béclère, Moutier (6)). They found "that the folds were constituted by a vasculo-connective-tissue axis covered by mucosa; the *muscularis propria* does not participate in their formation. It was also noted that the puckering is never caused by follicular hyperplasia or lymphoid proliferation. One simply noted, in certain cases, at the base of the folds, besides at their summit, a thickening of the *muscularis mucosae.*"

The gastroscopic observations have often been recorded by photography through the gastroscope (Henning (7, 8), Schindler (17)). Pictures by means of the "gastrophotor" are of questionable value because they are taken blindly, not knowing which way the apertures point (16).

The gastroscopic observations of the interior of the stomach are as follows: The cavity of the antrum does not show any folds as mentioned above. The peristaltic contractions run over the wall as circular protrusions. The folds of the posterior wall are much larger than those of the anterior wall. Apparently this fact is not only caused by the greater distance of the objective from the mucosa of the anterior wall, but it is, also, observed in the beginning of the examination when the anterior wall is very close to the objective. The folds of the posterior wall are not so regular as they are seen in the X-ray relief pictures. Gastroscopically the folds are generally longitudinal, joined by many cross folds and are "fork-like" (Henning). They are more numerous than the X-ray reveals. Often they are much distorted and form a network. This network is a very common finding in the anterior wall. Here the folds are much more delicate than on the posterior wall. In the greater curvature, the folds are more regular and parallel than in the other portions of the stomach. A prominent fold which separates the greater curvature from the anterior wall has been described by Henning, but I have not regularly seen this. Even in the greater curvature the folds are generally serpiginous. The upper lesser curvature which is seen on a tangent appears as an overhanging fold, but there is in reality no fold. On the contrary, the lesser curvature, in which the folds of the "magenstrasse" (Aschoff (1)) might be expected to be seen, is the smoothest part of the whole stomach. In special cases, some flat parallel folds are observed. The network of folds is very regularly *found*

in the fornix. The formation of the *m. sphincter antri* with its crossing folds has already been described.

On the whole, the normal mucosal folds as seen gastroscopically are much more delicate, more numerous, and more irregular than those seen in X-ray relief pictures.

SUMMARY

1. Gastroscopy gives important information with regard to the gross anatomy of the stomach and in many respects amplifies and alters the concepts gained through anatomic and roentgenologic research.

2. The interior of the stomach is separated into two distinct cavities: that of the body and that of the antrum by the marked *musculus sphincter antri.*

3. The *m. sphincter antri* is situated at the level of the "angulus" of the stomach, but is a separate entity from the "angulus." It has a cord-like appearance. It is probably formed by a circular contraction of the *muscularis propria* which is crossed by oblique folds of mucosa.

4. The paristaltic waves in the antrum do not begin at the *m. sphincter antri,* but at different points distal from it.

5. A nomenclature adapted to these facts is suggested.

6. The pylorus is mobile. In the left side position it falls toward the anterior abdominal wall. In some cases it may even reach the left side of the abdominal cavity, so that pylorus and cardia lie in a sagital plane.

7. The position of the stomach is chiefly influenced by the body build. The position of the body, fullness of the intestine, and the movements of the diaphragm also affect the position of the stomach.

8. The posterior wall of the stomach always forms an angle with the axis of the esophagus, so that the posterior wall runs toward the anterior abdominal wall. This angle may be stretched by mechanical means in about 50% of all cases. It is greater than 34° in about 7% of all cases.

9. The mucosal folds of the stomach are best observed by gastroscopy. They form a delicate, irregular network which is much more marked in the posterior wall than in the anterior wall, usually absent in the lesser curvature and always absent in the antrum. These delicate folds do not seem to correspond completely with the X-ray relief findings.

10. In this paper the gastroscopical findings are compared with anatomical and roentgenogical findings.

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Relationship of Histologic and Gastroscopic Findings in the Diagnosis of Chronic Gastritis: A Brief Review

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THE Pathologists (Knud Faber (3), Konjetzny (11), Paschkis and Orator (16), etc., call the mucous membrane of a stomach normal only when no interstitial cell infiltration whatever is seen. The main experiments and sections have been made in newborn infants. Such a type of stomach, however, has been found also in older children and in adults. Paschkis and Orator found in an extensive number of autopsies only 10 stomachs which could be called "normal"; so that practically no adult had a normal stomach but everyone had a chronic gastritis. This conception does not correspond with our clinical conception of a disease (Katsch (10)). The fundamental problem of medicine: "what is a disease?" is profoundly affected by the above mentioned statements.

In my opinion an adult who does the hardest work, who enjoys life without any restriction, who never has any troubles from the stomach or of other organs, who in the immediate future does not develop such troubles from an already present but silent or incipient disease, cannot have a diseased stomach.

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In the skin, for instance, a scar is not a disease although it is not "normal"; the anthracosis of the lungs is not present in the newborn, but is not a disease in the adult (except some special cases); we have learned that the appendix may show some cellular infiltration even though its owner is healthy, so that we have not the right to extirpate such appendices.

If we should accept the above mentioned definition of the pathologists we should lose at the same time the clinical significance of the entity "gastritis" which has been established after such long efforts. On the other hand, we must admit that there are many stomachs which show such marked histological changes, especially tremendous interstitial infiltration that a pathologic process is evident. In these cases we never have to deal with healthy adults but with suffering patients.

In accordance with the conception of the pathologists, almost every adult should suffer either from subjective or objective symptoms. The coincidence of such symptoms with the well known "histo-pathologic changes" is naturally not conclusive of a causal connection. This is, however, too easily forgotten. Knud Faber, for instance, quotes Bennet and Ryle (1) who found among 100 apparently healthy students four cases of anacidity. He believes that such a fact is often regarded in England as decisive proof of the existance of an inborn constitutional anacidity. "But," he asks, "how do we know it is inborn? It may just as well be a state subsequent to an acute gastritis." This is evidently correct. As almost all adults show some histological state of "gastritis," one should expect even a much higher percentage of anacidity. Thus there is even more probability that the theory of the "constitutional" anacidity is correct. Nevertheless Knud Faber forgets a third factor which has been proved with the greatest exactitude, namely the influence of psychogenic stimuli upon the secretion of stomach juice (Pavlov (17, 18), Heyer (8), etc.)). It is astonishing that not more of these young adults show a lack of free hydrochloric acid because the introduction of a stomach tube is so often connected with feelings of disgust and apprehension. Although a chronic gastritis in these four cases perhaps was present it has not been proved.

Thus we see that the anatomical conception of today of chronic gastritis disagrees with the clinical conception. An agreement could be reached only if it would be possible to draw anatomically a sharp line between those adults who are suffering from their stomachs and those who are not. It is so extremely difficult because the material is not available. Healthy persons do not die and it is almost impossible to exclude the possibility that the stomach has been affected by other diseases present. We hope that biopsies may later settle these questions. It will, however, not be easy to obtain permission to carry out biopsies in many healthy people.

The other method which has demonstrated the frequency of chronic gastritis; *i.e.* gastroscopy, works under quite different conditions. They are partly more favorable, but gastroscopy also has its disadvantages. That it is a subjective method does not counteract its scientific value. We are certainly spoiled by the objective documents of the anatomists and of the roentgenologists. If the conscious subjective observation would be without value, Laennec's discoveries, the whole development of ophthalmology after the invention of the ophthalmoscope, the development of urology, proctology, etc., would have been impossible. The hope that photography would help has not been fulfilled. The author has proved this in several papers. In gastroscopy, however, the most careful observation does not protect against errors. It is significant that the author believes that he saw numerous gastric ulcers without any extensive gastritis, while Korbsch (13) believes he observed extensive gastritis in each case of ulcer. It is, furthermore, not only possible but very likely, that very slight changes are overlooked with the gastroscope, which, as is well known, pictures important parts of the stomach wall in reduced size.

On the other side, gastroscopy has decisive advantages: it enables one to study carefully, and repeatedly, stomachs of people who are capable of doing heavy work, enjoying their lives to the fullest extent. The author has made one series of such examinations in Europe. There were always some healthy young girls or old men ready to be gastroscoped for a few marks; they were often observed as a check in the establishing of the method and also, still later, in the numerous gastroscopic courses during which the students introduce the gastroscope in them. In this country this important method of examining normal people seems to be more difficult. A very good knowledge of the "normal" mucosa, as seen through the gastroscope, was established in this manner. The author believes that he knows exactly when some parts of the mucosa do not look like those of normal people. In contrast to the anatomic conception, he found that all those persons with abnormal appearances of the stomach mucous membrane were invariably suffering from stomach disorders or other diseases affecting the stomach (pernicious anemia, etc.). The changes seen through the gastroscope have been described elsewhere. If they were controlled microscopically (after operations) regularly very marked changes were found.

CONCLUSIONS

If we compare the two methods, histologic and gastroscopic, regarding their value for the establishment of the entity; "chronic gastritis," we find:

(1) The positive findings in histology do not prove the existence of a clinical "disease" of the stomach. Almost every adult shows some interstitial changes in the stomach mucosa as compared with the newborn. To say that ulcer, cancer, or blood diseases, etc., are the result of such histologic changes is permissible only when the changes are very marked.

(2) Gastroscopy allows repeated study of the interior of quite healthy individuals and the establishment of a morphologic endoscopy for the normal stomach. Changes of this picture prove, with greatest certainty, the presence of an organic lesion, especially of chronic gastritis. Minor pathologic changes are of the highest clinical and scientific significance.

(3) A method to harmonize anatomic and gastroscopic findings urgently is needed.

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Intragastric Photography*

By

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THE visualization of the inner surface of the stomach as a clinical procedure has been the objective of all gastro-enterologists. This was partly realized when Mickulicz in 1881 reported the first successful use of the gastroscope. Since then, the instrument has been greatly improved first by Rosenheim, later by Elsner, Schindler, Einhorn and Chevalier Jackson. Nevertheless, the inherent danger of passing a rigid tube through the esophagus cannot be overcome.

About the beginning of the present century, roentgenography was introduced and soon almost entirely displaced gastroscopy. The roentgenogram, however, is merely a shadow picture of the organ studied. Abnormal changes may be observed readily because of its distinct outline. Yet, lesions of the anterior and posterior walls of the stomach and of the cardiac region are frequently missed because of the contained barium mixture which completely covers these areas. Also, shallow ulcers and small infiltrated areas on the lesser and the greater curvatures often are overlooked; in fact such lesions are very difficult to diagnose by either fluoroscopy or films. Mucosal "relief" studies more recently have been introduced which, in the main, have added little to our knowledge. Mechanical pressure exerted against the stomach walls is not a normal condition. Since only a small amount of barium mixture for "relief" films or the "compression" technique, is used, the stomach is practically in a collapsed state causing the mucosal folds to overlap, thus often concealing a small ulcer.

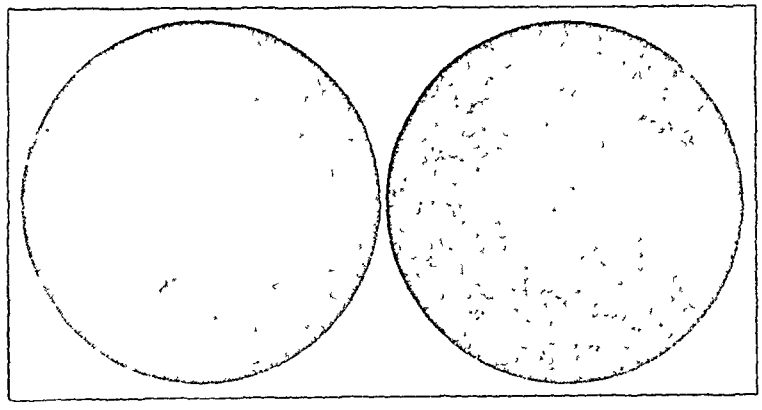


Fig. 1. Picture of normal gastric mucosa. Refracted spots due to contained mucus.

Within recent years attempts have been made to revive the use of the gastroscope. But even with the modern technique the entire procedure is time-con-

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suming and requires the skill of a highly trained expert. The best modern flexible instrument still presents numerous contraindications and its field of visualization is limited. A large portion of the lesser curvature and the posterior wall and almost all of the cardiac portion of the stomach are hardly ever seen. Another inherent defect in its use is that the instrument is not self-recording.

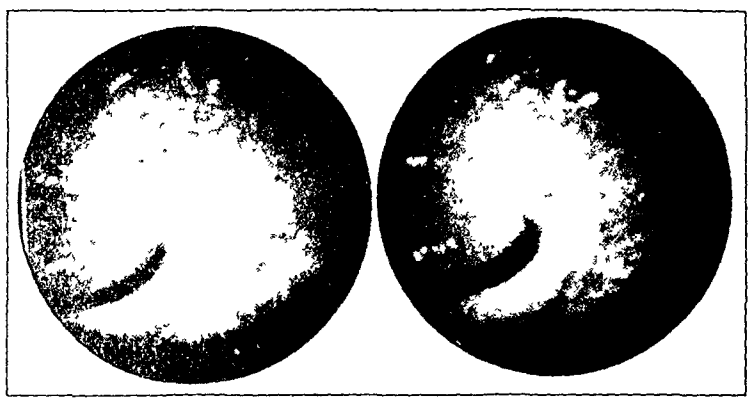


Fig. 2. Normal mucosa. Picture shows pyloric opening.

Intragastric photography with the camera in the stomach cavity would seem to offer a practical method by which the inner surface of the living stomach could be visualized. An instrument for this purpose was invented by Mr. Bach, with the clinical assistance of Professor Porges and Doctor Heilpern, at the Wenkenbach Clinic in Vienna. It was introduced into this country about six years ago. Since then, the gastro-intestinal department of the *Beth-El* Hospital has made constant use of this instrument. Our studies have included normal stomachs in patients who were admitted for conditions other than gastro-intestinal diseases, stomachs of patients in whom lesions were diagnosed by means of roentgenological examinations and stomachs of patients who gave symptoms of gastric lesions which could not be substantiated by roentgenography.

APPARATUS AND METHOD

The *instrument* for taking intragastric pictures consists essentially of a flexible stomach tube carrying at its distal end a tubular camera of about 30 French gauge, together with a small bulb for illumination so constructed that, when activated by current furnished by a special transformer, it yields an intense bluish white light of 20,000 candle power for 1/120 of a second. The camera carries eight films divided into two groups of four, each group photographs the entire circumference of the stomach at a different level. By means of two pin point holes placed before each film, pictures are obtained so that at one exposure eight stereoscopic photographs (sixteen pictures) are made. These eight films are marked so that one can readily tell which part of the circumference of the stomach is pictured on the film.

Intragastric photographs are best taken in the morning after the subject has fasted overnight. In our clinic the stomach is further emptied of its secretion by means of a Rehfuss tube; where there is pyloric stenosis with retention, the stomach is lavaged. The camera tube is then introduced in the same manner as an Ewald tube. In our experience, we have found that the use of the fluoroscope helps to localize the camera. The stomach is now inflated with air through a special opening in the tube, the shutter is opened and the films are exposed by flashing the lamp, the tube is then withdrawn. With our present technique, the whole procedure takes from twenty to thirty seconds. The camera is roentgen ray proof and the films are not fogged by the use of the fluoroscope.

The inflation of the stomach with air is necessary to give distance between the camera and the stomach wall, and also to smooth out the mucosal folds, thus rendering it possible to reveal hidden lesions. The air-inflated stomach has a tendency to approach more nearly the illustrations

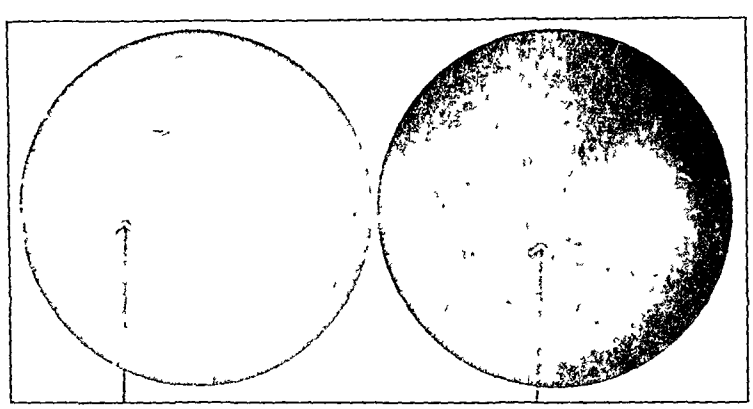


Fig. 3. Picture shows shallow gastric ulcer. X-ray was negative. History is pain with relation to food, also bloody vomiting.

of the stomach in the older anatomical text books. The fundus is higher, the greater curvature more to the left, and the pylorus somewhat lower. This is especially true in the orthotonic and hypotonic types of stomachs.

Intragastric photographs show the condition of the mucosal surface exactly as it appears. They reveal any defects which may be caused by erosions, ulcerations or growths, benign or malignant.

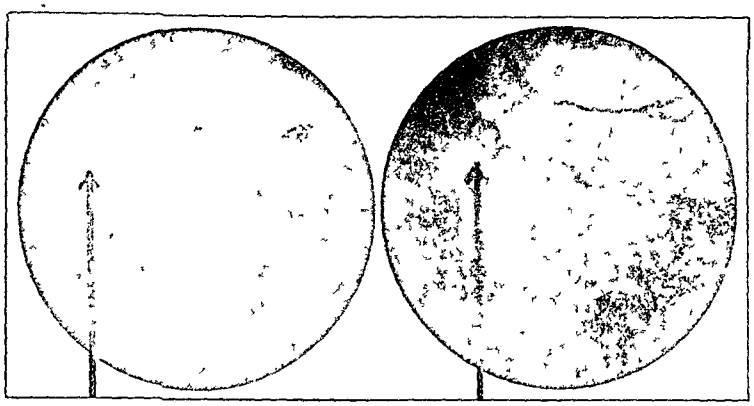


Fig. 4. Picture shows ulcer at pylorus X-ray diagnosis pyloric carcinoma. Patient improved under treatment. Hyperchlorhydria of gastric contents.

Skill in the interpretation of the resultant pictures may be acquired by studying the photographs obtained in normal and pathological stomachs and checking them against these specimens obtained by surgery or at autopsy.

The pictures taken in *normal stomachs* show normal sized rugae radiating along the axis of the stomach with some intertwining on the greater curvature. The pyloric canal is readily visualized In *chronic gastritis*, the rugae may be seen as markedly thickened ridges. The shallow *ulcer* is noted as a small crater with a ridge surrounding it, while the penetrating ulcer is shown as a deep crater with rugae drawn toward, or radiating from it *Tumors* appear as masses with regular or irregular outline.

AUTHOR'S STUDIES

In our first few attempts we had poor results but, as our technique improved, pictures became uniformly good. To date we have photographed the stomachs of 216 patients. All patients but two were roentgenographed either before or after the intragastric photographs had been made.

Roentgenography and intragastric photography agreed in the examination of 153 patients. Of these, fifty were reported as normal, fifty-two suffered from carcinoma of the stomach and fifty-one showed the presence of gastric ulcer (Figs. 1 and 2).

In seven patients the roentgenologist reported suspicion of carcinoma. However, the intragastric pictures were definitely positive. Three of these patients were operated upon and the diagnosis proven in each case

In the remainder of our series, both methods differed in their diagnostic pointings. In fifteen of these patients, the intragastric pictures showed the presence of *ulcer*, most of which were quite shallow (Fig. 3). Thirteen of these patients were roentgenographed with the diagnosis of pyloric carcinoma in two and with negative results in the remainder (Figs. 4 and 5). Three of this series were operated upon and the diagnoses by intragastric photography were confirmed. In the remaining ten patients, the diagnosis was substantiated by the history and subsequent clinical course.

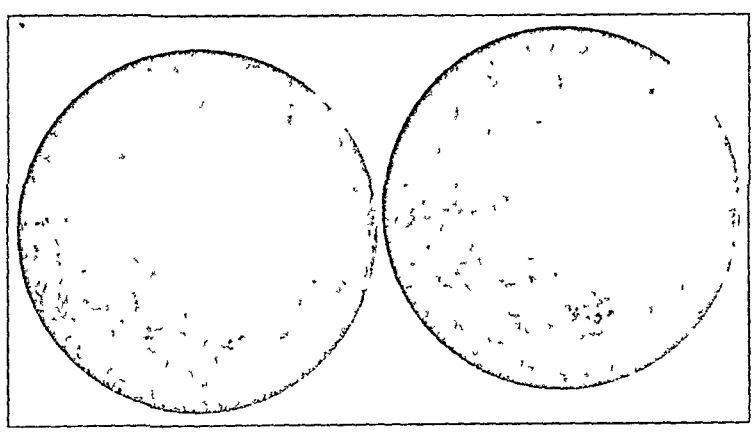


Fig. 5 Picture shows ulcer on lesser curvature. X-ray diagnosis carcinoma on lesser curvature At operation ulcer was found. Note rugae radiating from the ulcer in fan shape.

Chronic gastritis was diagnosed twenty-eight times. In twenty-seven instances the roentgenographic reports were negative. In one patient the report was carcinoma of the stomach. Operation proved the presence of marked hypertrophic gastritis with no evidence of carcinoma. The patient is alive and well two years after the operation (Fig. 6).



Fig. 6. Pictures show chronic gastritis. X-ray examination showed large defect on greater curvature, interpreted as carcinoma. Operation proved absence of carcinoma and presence of chronic gastritis. Defect was due to band constricting greater curvature.

Three patients affected with gastric carcinoma were correctly diagnosed by intragastric photography. This observation was proven by operation on two patients; the third died with evidence of carcinoma and metastases. In two of these subjects, the X-ray diagnosis was gastric ulcer; in one "no defect" was noted (Fig. 7).

On the other hand, in eight patients the roentgenographic examination showed the presence of ulcer which was not the finding from intragastric photography. One of these patients was operated upon but no ulcer was found.

In two patients who had been operated previously for gastric ulcer and a gastro-enterostomy performed, in each case, the roentgenograph showed patent stomata. The intragastric pictures, however, failed to reveal the site of the gastro-enterostomy. This may have been due to poor technique in locating the camera.

COMMENT

From the above studies, it may be concluded that intragastric photography is a valuable adjunct as a diagnostic procedure in all cases of suspected or of obscure gastric lesions. As reported above, it has demonstrated its usefulness in cases where lesions were suspected but could not be proven by roentgen methods. Shallow mucosal ulcers often readily were demonstrated by the intragastric camera when such were not even suspected after the roentgenogram examination.

Intragastric photography should prove useful in the diagnosis of early gastric tumors, especially malignancies, at a stage when it is difficult to demonstrate such lesions by roentgenography. The procedure is a very useful aid in the diagnosis of chronic gastritis, whereas roentgenograms practically are of no value in that condition. By this new diagnostic method we are enabled to photograph the living mucosa directly and consequently should be able to establish the presence of objective damage. In our series of patients, frequently we were able to diagnose chronic gastritis,

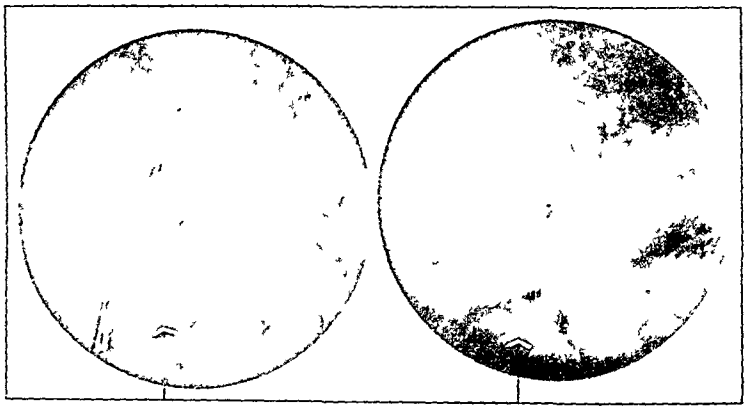


Fig. 7. Picture shows presence of tumor near pylorus. X-ray report was stenosing ulcer at pylorus. Operation proved presence of carcinoma.

often with superficial mucosal ulcerations, existing either as a clinical entity, or associated with such other pathological conditions as gastric and duodenal ulcer and cholecystitis. It should be possible to differentiate the atrophic from the hypertrophic type of chronic gastritis by means of these photographs. (Footnote).

However, it will take considerable time to fully appreciate the value of intragastric photographs and the method itself. As our experience increases, the technique will be greatly improved and our ability more complete to interpret the resultant pictures and to diminish the errors in diagnosis previously made. In this respect, intragastric photography is comparable with roentgenography in its early phases of clinical use. It is not expected that the procedure ever will replace the roentgen ray or other well established clinical methods used now in the examination of the stomach but it should prove of great help in more clearly or definitely making diagnoses in obscure instances.

Footnote: If the films or the prints, obtained by intragastric photography, are studied carefully by a hand glass giving moderate magnification, interesting and not altogether unimportant, additional pathologic changes become evident.—*Editor.*

The Origin, Fate and Significance of the Serum Enzymes

By

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BECAUSE they play an important rôle in normal digestion, and because, unquestionably, they are a factor in the etiology of food allergy, the pancreatic enzymes are assuming an increasing significance in the diagnosis and treatment of gastro-intestinal disturbances. There is need for a practical, reliable test for determining the function of the pancreas. Differences in methods, tests, terminology, and a lack of normal standards, are some of the reasons why a test for determining the pancreatic index is not now routine practice. In other papers (1, 2) we have given our reasons why we do not believe that any test for determining the pancreatic function, based upon a determination of the concentration of enzymes in the duodenal secretions, can give a true picture of the total, daily secretion of the pancreas. We have shown that, in health, the blood always contains the three pancreatic enzymes in a definite and constant concentration, and it is only in the serum that we can accurately determine the pancreatic index.

Likewise, the question of the therapeutic value of the pancreatic enzymes when given by mouth, is in a state of confusion. Elman and McCaughan (3) for example, do not believe that absorbed amylase plays a part in maintaining the serum level of amylase. Zucker, Newberger and Berg (4) deny the absorption of amylase. Crandall (5) believes that absorption of minute quantities of amylase is probable. These reports are precisely contrary to our findings. We have found that all three pancreatic enzymes are completely absorbed, even when given in excessive dosage (200 grains of an active extract, containing all three enzymes). Our findings have been so definite and we have obtained the same results so many times, that we believe that these differences can only be due to differences in tests and methods employed.

Crandall's work was done principally on dogs with fistulae. In our opinion any external opening destroys the "closed system" upon which depends the pancreatic secretory mechanism. We have evidence which indicates that the normal secretion of the pancreas is regulated by a mechanism dependent upon a chemical equilibrium between the concentration of enzymes in the blood, and the concentration within the cells of the pancreas. When the serum concentration of enzymes falls below 0.2 by our test, enzymes pass from the pancreas into the blood stream; when the serum concentration reaches 0.2, the concentration in the blood and within the cells of the pancreas is in equilibrium and secretion ceases. This work will be fully reported in a later paper.

In former days, surgeons observed the rule: "When in doubt, always drain," but latterly they are commencing to appreciate the fact that prolonged, unnecessary drainage, because it carries out normal secretions, thereby upsetting the delicate chemical equilibrium by which glandular secretion is regulated, very often is the factor which makes for a fatal outcome. Studies made on frightened, injured, frequently infected animals, with the pancreatic secretory mechanism "open", cannot be expected to give a truly normal picture of the pancreatic enzyme concentration. Zucker, Newberger and Berg used the starch-iodine test (Wohlgemuth) which in our opinion, is worthless as a quantitative test for enzyme concentration. Most of our work was done on patients who were not disturbed more than is necessary to obtain blood from a vein. The taking of a small quantity of blood from a vein at the elbow, is so quickly and easily done, that the delicate secretory mechanism is unaffected, and we

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obtain a truly normal picture of the enzyme concentration in the serum.

In this paper we will briefly restate our position, report additional information not hitherto published, review the salient features of our test, and thus attempt to dissipate the confusion which now surrounds pancreatic diagnosis and therapy. It is only in this manner that we can ever hope to rationalize our differences, which we believe, can only be the result of differences in procedure.

THE ENZYMES IN NORMAL SERUM

Normal serum always contains serum amylase, which hydrolyzes all starches; serum lipase which splits all fats, and serum protease which hydrolyzes all proteins. These three enzymes are always found in a definite and constant concentration, which is uninfluenced by intake of food, sleep or exercise. Likewise, the serum enzymes are always found in parallel concentration, i.e., if one of them is present in a certain concentration, all are present in the same relative concentration. The normal serum concentration of serum enzymes is 0.2 by the test which we have suggested. In previous papers (1, 2) we have stated our belief that the pancreas normally secretes a sufficient concentration of enzymes to combine with all of the food taken, plus an excess which passes free into the blood stream. It is the concentration of these free serum enzymes which is determined by our test. Every cell in the body is thus protected against whole, unracemized foods by these buffer serum enzymes, which prevent any food from reaching the cells in an unsplit state which cannot be used as food.

METHODS

In our opinion, the best test for amylase is a determination of the reducing sugar liberated from a given quantity and percentage solution of soluble starch by 0.2 c.c. serum, when incubated at body temperature for a given period. The menstrum, of course, must be correct for optimal enzyme activity. This test, however, is only accurate when a spot test is finally made to determine accurately the end-point when reduction of Fehling's solution is complete. (One drop of solution to be tested; one drop of 5% acetic acid; plus one drop of 10% potassium ferrocyanide. Incomplete reduction of copper gives a brown film.)

The concentration of lipase is determined by finding the quantity of fatty acid set free when 0.2 c.c. serum is incubated at body temperature for a given period with ½ c.c. of any neutral food oil (corn or olive oil). The quantity of acid is determined by titrating against .02 normal sodium hydroxide. The concentration of trypsin is determined by finding the quantity of fibrin which is completely hydrolyzed by 0.2 c.c. serum when incubated at body temperature for a given period. For this purpose, we fashion fibrin into cylinders of standard length and diameter, by mixing powdered fibrin with warm water and pressing the mass through a glass pipette. The cylinders are standardized by determining the length of cylinder which is completely hydrolyzed by 0.2 c.c. normal serum when incubated at 98.6 for 24 hours.

But because the serum enzymes are always secreted in parallel concentration, previously pointed out by us and later verified by Baxter (6) the serum concentration of enzymes can be more easily and accurately determined by finding the concentration of amylase alone. If amylase is present in a certain concentration, all three pancreatic enzymes are present in the same relative concentration. Because there exists confusion concerning the difference between our test and the older starch-iodine test, we will at this point, briefly restate the technique of the newer test. The test, together with a discussion of the involved chemistry, has been described in detail elsewhere (7).

Test for Determining the Pancreatic Index (Test for Food Allergy)

The reagent: Make a 5% suspension of *starch cells (Argo) in distilled* water. To each ounce add 4 drops of Lugol's solution from a medicine dropper. Shake. Under the microscope the starch cells will be seen stained blue-black, each cell containing a definite quantity (the "just right" quantity) of starch-iodine compound.

The test: To each of six small test tubes, add 1 c.c. reagent. To successive tubes add respectively, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6 c.c. serum. Shake and incubate for 24 hours in the warm air incubator (not the water bath) at 98.6.

The reading: When the test is set up as above, the starch cells settle to the bottom of the tube in a black mass. That tube in which the black mass at the bottom of the tube *turns completely white* in 24 hours is the reading. The normal pancreatic index by this test is two-tenths (0.2). The number one tube is the control. If the number 6 tube turns completely white, while the other tubes still contain varying quantities of black at the bottom, the reading is *minus* 4 (6 minus 2 equals minus 4). If the number two tube "goes over" (turns completely white) the serum enzymes are present in normal concentration and the patient is not allergic to food. On the other hand, a pancreatic index of minus 4 indicates that the serum enzymes are present in reduced concentration and the patient is allergic to food. Because the serum enzymes are always present in a constant concentration, blood may be taken at any time.

It will thus be seen that the newer test differs from the older test in that the iodine is fixed by the starch until liberated by the amylase, when it immediately combines with the intermediate products of hydrolysis. Because free iodine is never present, the reaction continues on to completion. The test is a moving titration of hydrolysis as it proceeds—in the test tube and also in the blood stream.

In the older test, when used quantitatively, it is impossible to distinguish between the colors imparted by small quantities of starch and iodine, and the color imparted by iodine itself; while in our test the color changes are distinct—from jet black to white. The newer test is a cross section of hydrolysis as it takes place in the blood stream; a cleancut, visual method for titrating hydrolysis from beginning to end.

ARE SERUM ENZYMES PANCREATIC ENZYMES?

Enzymes which are functionally identical with the pancreatic enzymes, are found in the serum, urine, feces, and in extracts of every organ and tissue of the body, except the heart and brain. That all of these enzymes are pancreatic enzymes would seem to be indicated by the fact that their concentration can be influenced by the administration of an extract of whole pancreas. The normal serum concentration of enzymes is 0.2 by our test, and cannot be made to go above this level. If a patient with a pancreatic index of minus 4 is given 10 grains of an extract of whole pancreas, the serum concentration is restored to normal in one hour. If a massive dose (200 grains of the whole extract, containing all three enzymes) is given at one time, to a patient with a normal index, and hourly titrations of serum and urine made, it will be found that the serum concentration remains normal, while the urinary concentration falls approximately 50% in one hour. These observations indicate a definite relationship between the exhibition of pancreatic extract and the serum and urinary concentrations of en-

zymes. The prompt manner in which an active extract of whole pancreas influences the blood and urinary enzyme level, would seem to indicate that the pancreatic enzymes are absorbed from the gastro-intestinal tract, and that the serum and urinary enzymes are in fact, pancreatic enzymes.

THE ABSORPTION OF PANCREATIC ENZYMES

That the pancreatic enzymes, when given by mouth, are absorbed in the active state, would seem to be indicated by the following observations. If 10 grains of an active extract of whole pancreas is given to a patient with the highest degree of pancreatic hypofunction, (minus 4) the serum concentration will be restored to normal in one hour. Thereafter, it will gradually fall to the previous level. If a larger dose is given (50 grains), the serum level will be restored to normal in one hour and remain normal for approximately three days, when it will gradually fall to the original level. These observations indicate that pancreatic extract is absorbed, and that when taken in quantities in excess of that necessary to restore the normal serum level, the excess is stored, and later liberated in such concentration as to maintain the normal serum level. The serum level cannot be made to go above two-tenths (0.2) by our test. When the larger dose is given (50 grains) the urinary concentration always falls approximately 50% in one hour, while the concentration in the feces is unaffected. In short, when given to a patient suffering from pancreatic hypofunction, pancreatic extract restores the normal serum enzyme level; when given to a normal patient, the serum level is unaffected. Likewise, the concentration in the feces is unaffected, while the urinary concentration is reduced. These observations indicate that the pancreatic enzymes are not eliminated in the urine or feces. We do not believe that the enzymes are eliminated by any channel, in the sense that truly foreign substances are eliminated from the body. If the urinary enzymes were true excretion products, an increased intake of enzymes would be followed by an increase in the urinary concentration. Their presence in the feces can easily be accounted for, but we have no explanation as to the significance, if any, of the decrease in the urinary concentration, following administration of large doses of pancreatic extract. Evidently, the kidneys exhibit toward the enzymes a selective permeability, which decreases in the presence of an increased concentration of enzymes.

THE RELATION OF THE SERUM ENZYMES TO THE SPLEEN AND LIVER

As stated above, if 50 grains of pancreatic extract are given to a patient with a normal pancreatic index, the serum concentration remains unaffected; the concentration in the feces remains unchanged, while the urinary concentration decreases. What then becomes of the extract? Is it destroyed—digested, so that we no longer find the enzymes in the active state, but in a form which is indistinguishable from other proteins? Are they stored somewhere in the body? In order to determine this last possibility, the following experiment was undertaken.

One group of rabbits from the same litter were given 30 grains of pancreatic extract daily for one week. The animals then were sacrificed and, together with control animals, all organs were ground with quartz sand and extracted with distilled water. The extracts were neutralized and titrated for enzyme concentration by the methods previously outlined. The concentration of enzymes in the livers of those animals which had received pancreatic extract in excessive dosage, was approximately twice that in the control animals, while the spleen contained a concentration averaging 17 times greater than the control animals, indicating that when given in excessive dosage, the pancreatic enzymes are stored in the active state in the liver and spleen. The fact that the serum concentration remains normal for several days when a subnormal patient is given an excessive dose of pancreatic substance, would seem to indicate that the stored enzymes are released from the spleen and liver in such concentration as to maintain the normal serum concentration.

Finally, we will close by asking a question. It has been definitely shown by a number of workers (Alvarez, Walzer, etc.) that whole proteins normally pass into the blood stream and are regular and normal constituents of serum. What then becomes of them? What, normally, is their ultimate fate? Why are we not all food sensitive all of the time? We believe that the serum proteins are split by the serum enzymes, and that a reduced serum enzyme concentration explains allergy to foods. Clinically, the administration by mouth, of an active extract of whole pancreas, has been found to be effective by the writers, and by a number of other careful clinicians.

CONCLUSIONS

1. Normal serum always contains serum amylase, lipase and protease, in a constant concentration of 0.2 by the test which we have suggested.
2. We believe we have shown that the serum enzymes are in fact, pancreatic enzymes.
3. When given by mouth, the pancreatic enzymes are absorbed in the active state.
4. The normal concentration of serum enzymes cannot be increased by the administration of pancreatic enzymes.
5. Pancreatic hypofunction is quickly corrected by the administration of an active extract of whole pancreas.
6. When given in excessive dosage, pancreatic extract seems to be stored in the liver and spleen, from which organs it is liberated in such concentration as to maintain the normal serum level.

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SECTION II—*Experimental Physiology*

Daily Variations in the Concentrations of Acid and Pepsin in the Gastric Juice of Three Persons Observed for Two Months*

By

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FOR fifty years and more physicians have been depending for diagnostic aid on a single gastric analysis, seldom stopping to find out how different the figures might be if a second or a third analysis were to be made on successive days. In 1931 we tried to fill this gap in medical knowledge by studying the variations in acidity which took place in the gastric juice of two young women observed daily for a month (1).

One of these women, who was nervously stable, had a fairly constant gastric acidity except at the end of the period of observation, when she became excited over the prospect of her approaching vacation trip. Then there was a big variation from her normal. The other young woman, who was less stable emotionally, reacted to a severe disappointment with large swings up and down in the curve representing gastric acidity. As a result, there were many days during the month when a single gastric analysis would have been worse than useless as an index to the normal activity of her gastric mucosa.

Recently, while studying the effect of a diet deficient in vitamin B_1, the senior writer had the opportunity of studying for two months the concentrations of acid and pepsin in gastric juice removed almost every day from the stomachs of two women and one man. The nutritional aspects of this experiment will be described elsewhere, and in this place we will record only the extent of daily variations in the gastric juice, together with a few other data. Because the deficient diet did not seem to have any effect on gastric secretion, it seems probable that the daily variations observed in these three persons closely resemble those that might be found in anyone living on a normal diet.

In Figure 1, the three sets of curves represent concentrations of acid and pepsin in gastric juice obtained from the three persons studied. It will be seen that with both acid and pepsin there was least variation in the case of the man, Dr. P. Interesting is the fact

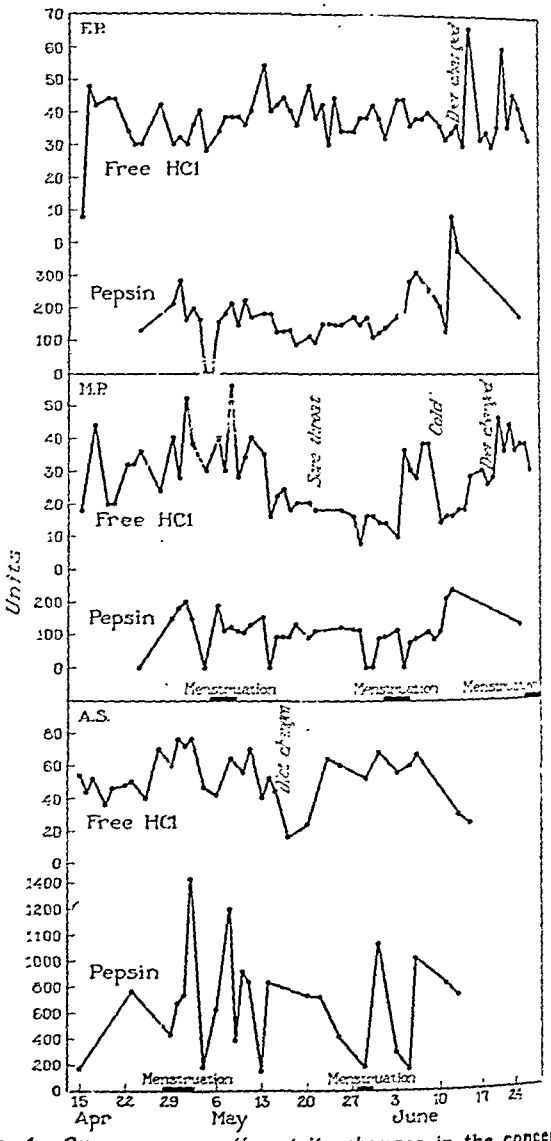


Fig. 1. Curves representing daily changes in the concentration of acid and pepsin in the gastric juice of three persons studied for two months

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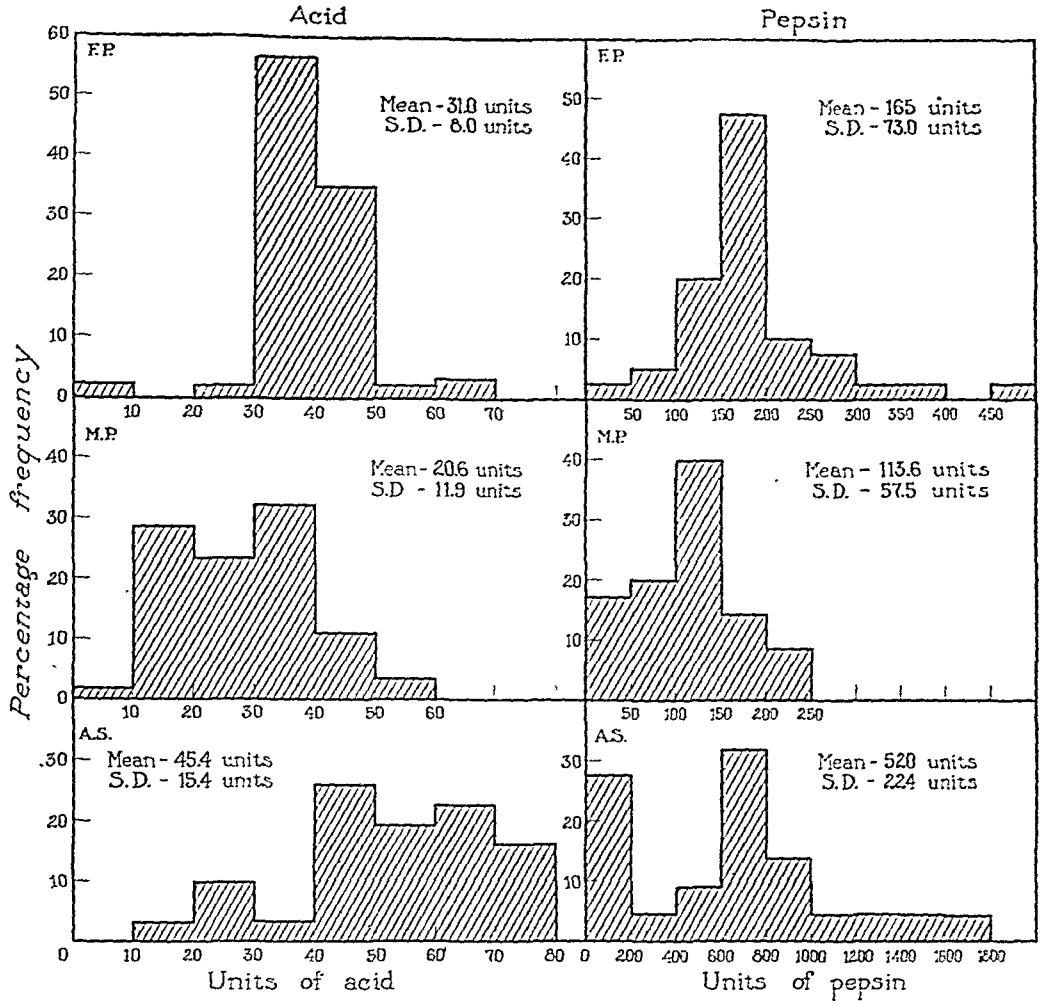


Fig. 2. Polygons showing for each of the three persons studied percentage distributions of the concentrations of acid and pepsin found in the gastric juice.

that in his case, the first measurement of acidity made, and the only one which would ordinarily have been available to a physician examining him, was very low and different from all subsequent values obtained. Interesting also is the fact that there were spectacular rises in the concentrations of pepsin and acid when this man, who for six weeks had been hungry, was told that he could stop the experiment and eat all he wanted.

In the case of Mrs. P. the two marked drops in acidity were associated with respiratory infections. We have as yet no explanation for the one big upward swing in the curve representing concentration of pepsin.

Miss S. was markedly tempermental, and the curves representing concentration of acid and pepsin in her gastric juice seem to reflect, in their irregularity, her mercurial nature. In her case, the curve representing concentration of pepsin is much more irregular than that representing acidity.

Incidentally it may be worth noting that, in the case of this woman, each of the three marked dips in the curve of free acidity appeared about eleven days before the onset of a menstrual period. There was no sign of any such cyclic difference in the gastric acidity of either Mrs. P. or of the two women studied by us in 1931.

Figure 2 shows the distributions of the concentrations of acid and pepsin observed in the case of the three persons. There, from simple inspection, it appears that data from Dr. P. showed the least variation; data from Mrs. P. came next, and data from Miss S. came third, with the greatest variation.

For concentrations of pepsin, the standard deviations in the three cases were 73, 57.5, and 224, respectively. The fact that these values are about half the size of the corresponding means shows again how wide the variation is when pepsin is measured repeatedly in one person. For acidities, the standard deviations were 8, 11.9, and 15.4. In the case of the two persons studied in 1931, the corresponding figures were 6.6 and 8.7.

Although at first glance there seemed to be little if any correlation between the concentrations of acid and pepsin in a single sample of juice, calculation showed coefficients of correlation of +0.528, +0.124, and +0.360 for data from Dr. P., Mrs. P., and Miss S., respectively.

SUMMARY

There were marked daily variations in the concentration of acid and pepsin in the gastric juice of three

persons who were studied almost every day for a period of two months. At times when these variations were great, one gastric analysis or even three or four made on successive days would have given a decidedly misleading idea of the usual ability of the particular stomach to secrete acid and pepsin.

The variability in gastric secretion was different in three persons studied. The evidence suggests that the greatest degrees of variability are to be found in nervous, impressionable, and temperamental persons who react too much to their environment.

It is conceivable that the big daily changes in the digestive power of the gastric juice which take place in nervous persons can at times have deleterious effects on the mucous membranes of stomach and duodenum.

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The Influence of Mucoitinsulfuric Acid on Peptic Digestion*

By

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IT was recently reported that peptic digestion can be greatly inhibited by commercial "gastric mucin" and by chondroitinsulfuric acid (Babkin and Komarov, 1932; Bradley and Hodges, 1934; Zaus and Fosdick, 1934). On the other hand, sufficiently purified preparations of mucoproteins, such as submaxillary mucin and mucin isolated from the alkaline or neutral gastric secretion of a fasting animal, failed to inhibit peptic activity in the early stages of digestion. Some inhibition could be observed, however, after more prolonged incubation.

Commercial "gastric mucin" was found to be a very composite mixture of many substances—chiefly products of the peptic digestion of mucoproteins—and appeared to be especially rich in mucoitinsulfuric acid. As a hypothetical explanation of the above observations the theory was advanced (Babkin and Komarov, *l.c.*) that the agent responsible for the strong inhibitory action of commercial "gastric mucin" on peptic digestion is mucoitinsulfuric acid and that the delayed inhibition of peptic digestion observed in experiments with purified mucoproteins is also due to the liberation of the same substances in the course of digestion. However, up to the present no direct evidence in this respect has been available owing to the difficulties experienced in obtaining sufficiently pure preparations of mucoitinsulfuric acid from gastric mucus.

According to Levene (1925) chondroitinsulfuric acid is a body closely related to the group of mucoitinsulfuric acids, yet these two groups of conjugated sulfuric acids are *intrinsically distinct*. Moreover, even in the group of mucoitinsulfuric acids the individual representatives exhibit decided differences in their properties. It is obviously important to ascertain the effect which the particular mucoitinsulfuric acid derived from gastric mucin would exert on peptic digestion. The need for such a study is accentuated by the fact that mucoitinsulfuric acid has recently been demonstrated (Komarov, 1935) to be an integral part of the protein complex of canine gastric juice.

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MATERIAL AND METHODS

The present report is based on a study of the effects produced on peptic digestion by four preparations of mucoitinsulfuric acid. One of the preparations was isolated from gastric juice in the form of sodium salt (preparation 1 of Komarov, 1935). The other three preparations were isolated in different ways from commercial gastric mucin (*Wilson Laboratories*). The methods of isolation and a full account of the analytical data will be reported elsewhere. All our preparations exhibited the general properties characteristic of mucoitinsulfuric acid derived from gastric mucus, as described by Levene (1925). It should be especially emphasized that they did not give the biuret reaction and did not contain phosphorus. The values for C, H, N and S were found to be entirely within the range for the preparations of mucoitinsulfuric acid obtained from various sources, as reported in the literature (Levene, 1925; Lopez-Suarez, 1913; Alzona, 1914). The only material difference in the composition of our preparations was in the content of sulfur, this being 5.04, 1.65, 1.30 and 1.01 per cent for preparations 1, 2, 3 and 4 respectively. These data indicate that the above preparations are mixtures of mucoitinsulfuric acid and mucoitin in varying proportions. On the basis of their sulfur content these preparations can be regarded as consisting respectively of 74, 24, 19 and 15 per cent of mucoitinsulfuric acid, the rest being mucoitin.

As sources of pepsin several commercial preparations of pepsin (Parke, Davis, U. S. P. 1:3000 and 1:10000; and Merck) were used, as well as various samples of canine gastric juice collected under different conditions of stimulation from dogs with a Pavlov pouch or with a gastric fistula and oesophagotomy. The peptic activity was determined either by Mett's method or by titration after Willstätter and Waldschmidt-Leitz (1921). In the latter case the substrates used were soluble egg-albumen (Merck) and solutions of acid metaproteins prepared from egg-white. In most of the experiments preparations 2, 3 and 4 of mucoitinsulfuric acid were converted into sodium salt immediately before use by dissolving in distilled water and neutralizing with NaOH to pH 7.0. In the control samples, instead of mucoitinsulfuric acid, distilled water was used, or solutions of sodium sulfate and sodium chloride in amounts equivalent to the content of sulfates and chlorides as determined in the ash of the corresponding preparations. In all the experiments the titratable acidity or the pH was equalized, the latter by means of Sörensen's

(1912) M/10 citrate buffer solutions. Nearly a hundred such experiments were carried out; only a few typical examples are presented here as illustrations.

EXPERIMENTAL RESULTS

The main fact revealed by this investigation is that mucoitinsulfuric acid inhibited the peptic activity of all the commercial pepsin preparations so far studied

TABLE I

Experiment of May 2nd. Pepsin (Parke, Davis & Co., U.S.P. 1:10,000) and mucoitinsulfuric acid (preparation 3) were used. These substances, in quantities as shown, were dissolved in 10 c.c. of M/10 citrate buffer solution, pH 2.0. The peptic power was measured by Mett's method.

Sample	Pepsin mg.	Mucoitin-sulfuric Acid mg.	Peptic Digestion 20 hrs at 38° C. sq. of mm.	Inhibition % of control
1	10.0	15.0	7.3	19.0
Control	10.0	none	9.0	—
2	5.0	15.0	2.9	34.0
Control	5.0	none	4.4	—
3	2.5	15.0	1.4	39.0
Control	2.5	none	2.3	—

and of most of the samples of gastric juice. The effect of mucoitinsulfuric acid on the proteolytic activity of commercial preparations of pepsin is illustrated in Table I. Similar results were obtained with the other preparations of pepsin studied.

More attention, however, has been paid in this study to the effect of mucoitinsulfuric acid on the peptic activity of canine gastric juice. Certain differences were found in the action of our four preparations of mucoitinsulfuric acid in this respect. All these preparations, when added in doses of a few milligrams per 1 c.c. of gastric juice, produced as a typical effect a marked inhibition of the peptic activity; but the degree of inhibition thus exerted was found to depend on the purity of the preparations. The preparation with the greatest inhibitory power was preparation 1, which was isolated from gastric juice and contained 74

TABLE II

Experiment of July 25th. 10 c.c. of gastric juice were diluted with 80 c.c. of 0.05N HCl and 10 c.c. of 0.5N HCl. 10 c.c. of this mixture were added to each of the samples described below. The acidity was equal in all the samples, viz., total 66, free 56 m. eq. per l.

Samples	Peptic Digestion sq. of mm.		Inhibition % of control (sample 3)	
	20 hrs. at 38°	44 hrs. at 38°	20 hrs.	44 hrs.
1. 18 mg. Na salt mucoitin-sulfuric acid + 5 c.c. H_2O	0.36	7.3	64	19
2. 18 mg. Na salt chondroitin-sulfuric acid + 5 c.c. H_2O	0.36	7.3	64	19
3. Control: 5 c.c. H_2O only	1.00	9.0		
4. Control: 1 c.c. 0.02N H_2SO_4 + 1 c.c. 0.02N NaOH + 3 c.c. H_2O	1.21	9.0		
5. Control: 1 mg. NaCl + 5 c.c. H_2O	1.14	10.3		

per cent of mucoitinsulfuric acid and 26 per cent of mucoitin. The activity of this preparation was identical with that of chondroitinsulfuric acid (a preparation kindly supplied by Dr. P. A. Levene of the Rockefeller Institute). This is illustrated in Table II. Preparations 2, 3 and 4 were less active than chondroitinsulfuric acid, yet they were many times more active than commercial gastric mucin, from which they were isolated. These relations are illustrated in Table III. Our general conclusion from the whole series of similar experiments is that the inhibitory activity of the above preparations depends on their content of ethereal sulfates, the preparations containing more sulfur being decidedly more active in this respect. This indicates that only unbroken mucoitinsulfuric acid possesses a strong inhibitory power, whereas the first product of its hydrolysis—the mucoitin devoid of the radicle of sulfuric acid—inhibits the peptic activity to a lesser extent or perhaps does not inhibit it at all.

The inhibitory action of mucoitinsulfuric acid on peptic digestion does not depend materially on the physicochemical properties of the substrate. It could be observed not only in the cases where coagulated egg-white was used as a substrate (as in Mett's method) but also where solutions of egg-albumen or

TABLE III

Experiment of February 11th. Gastric juice was obtained from two dogs with a gastric fistula and oesophagotomy by means of sham-feeding. The water-clear secretion was filtered immediately and preserved in the ice-box for two days. For the experiment it was diluted with two parts of 0.025N HCl. 15 c.c. of this mixture were added to each of the samples described below.

Sample	Substance	Acidity Total	Acidity Free	Peptic Digestion 24 hrs at 38° C. sq. of mm.	Inhibition % of controls
		m. eq./l.			
Control	Gastric juice alone	65	54	27.1	
1	120 mg. Fogel-son's "Mucin"	72	46	16.0	41.0
2	50 mg. prepara-tion 3	69	55	16.0	41.0
3	20 mg. prepara-tion 3	67	55	16.0	41.0
4	20 mg. prepara-tion 4	67	55	23.0	15.0
5	20 mg. Na salt of chondroitin-sulfuric acid	65	52	13.7	49.5

of acid metaproteins were employed and the rate of digestion was determined by the method of Willstätter and Waldschmidt-Leitz.

When varying quantities of mucoitinsulfuric acid are added to the same amount of gastric juice, the degree of inhibition of the peptic activity is the greater, the greater the concentration of mucoitinsulfuric acid, but only up to a certain point, beyond which further increase in the concentration of mucoitinsulfuric acid is not accompanied by any additional increase in the inhibitory effect (see Table IV). In this connection it should be mentioned that in not a single experiment was the peptic activity entirely inhibited by mucoitinsulfuric acid even when relatively large quantities of this substance were used (e.g. 50 mg. to 1 c.c. of gastric juice containing 1.2 to 1.5 mg. of protein).

Although mucoitinsulfuric acid had a striking inhibitory effect on the peptic activity of all the commercial preparations of pepsin so far investigated, and of most of the samples of canine gastric juice, yet in certain kinds of gastric juice the peptic activity could not be inhibited at all. The samples of gastric juice

obtained in response to subcutaneous injections of histamine (in doses of 0.05 mg. per 1 kg. weight) were found to be especially resistant. Another kind of gastric juice, the peptic power of which frequently could not be inhibited by mucoitinsulfuric acid, was the secretion collected at the very beginning of sham-feeding and the very last portions of the secretion thus induced; these samples usually contained large amounts of visible mucus.

DISCUSSION

The sum of the experimental evidence at present available indicates that the inhibitory effect, which mucoitinsulfuric acid exerts on the peptic activity of commercial preparations of pepsin and of gastric juice, does not materially depend on its action on a substrate but is due rather to its action on the enzyme. The strongest arguments in favor of such a view are the facts that the degree of inhibition which could be produced by increasing quantities of mucoitinsulfuric acid had a definite limit for every particular kind of gastric secretion, and that the peptic activity of certain types of gastric juice could not be inhibited at all by this substance. Why certain kinds of gastric juice, in respect of their peptic activity, are resistant to the action of mucoitinsulfuric acid is not yet entirely understood. The investigation of this problem is being continued. Some data are available, however, with regard to the secretion provoked by histamine, which was found to be especially resistant in this respect. It was found (unpublished experiments of the writer) that the protein material present in the histamine gastric juice has a more pronounced mucin-like character than that of the secretion induced by sham-feeding. The former was found to contain in all the cases so far investigated a smaller percentage of nitrogen (about 12 per cent) and to show a higher reduction after acid hydrolysis (an average of 30 per cent glucose). Apparently, in this case, pepsin is already linked to mucoitinsulfuric acid and therefore is unable to react with additional amounts of this substance.

Evidence has been obtained (Webster and Komarov, 1932; Babkin and Komarov, 1932) that in normal, freshly secreted gastric juice, pepsin may be present as a mucoprotein or as a complex compound with mucoprotein. This hypothesis is further supported by the fact that mucoitinsulfuric acid has been isolated in considerable amounts from the gastric juice and also from the protein fraction of this secretion (Komarov, 1935).

In view of the above considerations it seems reasonable to conclude that mucoitinsulfuric acid plays an important *rôle* in the regulation of the peptic activity of the gastric juice.

TABLE IV

Experiment of August 13th. Gastric juice was collected from a dog with a gastric fistula and oesophagotomy after sham-feeding. It was immediately filtered and mixed with four volumes of 0.05N HCl. 10 c.c. of the mixture were used in each sample. Preparation 2 of mucoitinsulfuric acid was used as free acid in the amounts shown.

Sample	Mucoitinsulfuric Acid mg	Acidity Total (m eq./l.)	Acidity Free (m eq./l.)	Peptic Digestion 24 hrs. at 38° C. sq. of mm.	Inhibition % of controls
Control	none	78	58	27.0	—
Control	none	78	58	27.0	—
1	10	79	58	16.8	37.8
2	20	80	58	16.0	40.7
3	30	81	58	16.0	40.7
4	40	82	58	16.0	40.7
5	50	83	58	16.0	40.7

SUMMARY

Mucoitinsulfuric acid, isolated from canine gastric juice or from commercial gastric mucin, inhibits the peptic activity of various commercial preparations of pepsin and in most cases also the peptic activity of gastric juice. The mechanism of this effect and the possible *rôle* of the mucoitinsulfuric acid present in the gastric juice are discussed.

The writer gratefully acknowledges the helpful criticism and advice which he has received from Professor B. P. Babkin during the course of this work.

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Pyloroplasty, Gastroenterostomy and Partial Parasympathetic Denervation of the Pyloric Sphincter, and Their Relation to the Emptying Time of the Stomach*

By

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ALTHOUGH resection of the pyloric sphincter has been widely and successfully employed to shorten the emptying time of the stomach in cases of pyloric obstruction since before the report of Rammstedt (1), (2), (3), (4), controlled experiments done by different authors on the emptying time of the normal stomach after such and similar operations have led to conflicting reports. McCann (5) has rightly said that "a half century of experimentation has not solved the problem of the emptying of the stomach." From his experiments on dogs he implicated the entire pyloric portion of the stomach as the important mechanism for the gastric retention of food, but admitted that the sphincter was the most important part of it. His procedures involved resecting the pyloric sphincter for a distance of two to two and one-half centimeters. He found that such an operation served to retain less food in the stomach, "indicating that the efficiency of the mechanism for the proper retention of the meal had been impaired." Pannett (6) found after simple resection of the pyloric sphincter in cats that food passed into the duodenum more quickly and in greater amounts during the early stages of digestion, but he was unable to state whether or not this acceleration of the passage of food from the stomach was maintained until it was empty. Thompson (7) working on the effect of resection of the pylorus in dogs states, "Following resection of portions of the pylorus, the emptying rate was reduced below the preoperative emptying time, regardless of the grade of resection. The rate, however, was not reduced increasingly for each grade of resection. Absence of the pyloric sphincter, therefore, rather than the increase in diameter of the pyloric outlet, seems to be responsible for the result observed." Later in the same paper, however, he states, "Contrary to prevailing opinion and despite the fact that the pyloric sphincter regulates the emptying of the stomach and the admission of duodenal juices into it, resection of the sphincter, combined with Polya gastrojejunostomy, does not lower the acidity of the gastric content nor hasten emptying of the stomach. . . . The fact that widening of the outlet of the stomach does not shorten its emptying time is also contrary to the general conception." Hughson (8) reported that section of the vagus nerves in dogs either at the cardia or on the anterior and posterior walls of the stomach caused a decrease in the normal emptying time of the stomach under general experimental conditions. Fetter, Barron and Carlson (9) reported a distinct delay in gastric evacuation of dogs after section of the vagi just below the diaphram. Meek and Herrin (10) found that the average emptying time was at least three times as long as the preoperative normal emptying time after intrathoracic resection of the vagi at the level of the seventh rib.

The present paper contains data, which are a by-product of another series of experiments, showing that in dogs simple resection of the pyloric sphincter, supplementing it by gastro-enterostomy, or partially parasympathetically denervating it does not shorten the emptying time of the normal stomach, but rather, if anything, lengthens it.

METHOD

In nine dogs the averages of from 5 to 17 normal gastric emptying times per dog were determined fluoroscopically using the experimental diet we have used in all of our experiments on gastric emptying times (11), (12). The pyloric sphincters were then sectioned (Rammstedt operation) and the average emptying times were re-established. In five dogs after the average control emptying time was determined for each animal a posterior gastro-enterostomy was performed and the emptying time was again determined. It two of these dogs (B-II and B-IV, Table I) the pyloric outlet was ligated at the time of the operation; in the others it was left patent. In one dog the emptying time was determined before and after partial parasympathetic denervation of the pyloric sphincter. The denervation was accomplished by rimming around the stomach a centimeter proximal to the pyloric sphincter down to the mucosa and placing four anchor stitches to prevent undue retraction of the cut structures.

RESULTS

All of the results are summarized in Table I. The number of times the high and low values were obtained before and after each operation is indicated in order that a comparison of frequencies may be made in case they are of equal value. The average emptying time is recorded both in hours and in per cent of the normal, the latter to simplify comparison and to offset individual variations between different animals. The medians and modes are given in the last columns for comparison with the average. Note the relatively insignificant disagreements between the averages, the medians and the modes.

In only two cases were the average emptying times of the stomach decreased by any of the procedures. In

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all other cases there was an apparent increase. The exceptional decreases (A-IX and B-I) were about one per cent, which is not significant. The increases in emptying times were larger and more variable in the case of gastro-enterostomy, though even here most of the increases fell within the range of error of the method, which has been calculated as 8 per cent.

DISCUSSION

The figures for the gastric emptying times in our Table do not agree with those given by some authors. The type of meal used undoubtedly influences this time. We explain our somewhat longer emptying times on the basis of the meal used. We fed an adequate diet for a dog and it was given daily in amounts sufficient to maintain a small dog. In larger animals it was necessary to give accessory feedings. We have not been concerned, in this paper, with a determination of emptying times *per se* but rather with the relative emptying times before and after given operative procedures.

These results in no way contradict the clinical results usually obtained from Rammstedt operations. In such cases the emptying time is actually shortened but it is a matter of reducing a pathologically long emptying time to a physiologically normal one, beyond which, our results indicate, it is impossible to go.

Although not repeating McCann's results (5), these experiments serve to confirm his contention that the entire pars pylorica, rather than the pyloric sphincter solely, participates in the function of food retention in the stomach. Our differences seem to show that the pyloric sphincter is of even less significance than he supposes, although it is conceivable, of course, that the function of a normal sphincter might be taken over quickly by the remaining pars pylorica.

Pannett's results (6) were obtained on cats. Leaving aside any considerations of possible species variations, it is possible that his observations may have been applicable to our results also. We made no observations on the first appearance of food in the duodenum. We limited ourselves to a determination of the time at which the stomach was completely empty. Our results did not conflict with what he admits might have been his if he had continued his observations for a longer time.

In animals with gastro-enterostomy there seems to be little difference whether the pylorus is patent or ligated. There is a suggestion that emptying may be a little more rapid if the pylorus is left patent, though individual variations between different animals make this insignificant. The large increases and individual variations after operation are undoubtedly related to the position and size of the stoma and to the particular muscle fibers of the stomach which are interrupted to make place for it. We thought that because of the normal standing position of the dog an anterior gastroenterostomy might be more efficient than a posterior one. Our one attempt was not successful, however, as

TABLE I

Effect of pyloroplasty, gastroenterostomy and partial parasympathetic denervation of the pyloric sphincter on the emptying time of the stomach

Dog No	Number of Tests		High Values				Low Values				Average				Median		Mode	
	Before	After	Before		After		Before		After		Before		After		Before	After	Before	After
			Hrs.	No. of times	Hrs.	No. of times	Hrs.	No of times	Hrs.	No. of times	Hrs.	% of normal	Hrs.	% of normal	Hrs.	Hrs.	Hrs.	Hrs.
A. PYLOROPLASTY. (Rammstedt Operation).																		
I	6	2	8 75	1	9 50	1	7.25	1	9.00	1	8.00	100	9.25	116	8.00		8 00	
II	10	18	6.00	1	6 00	5	5.00	3	5.00	1	5.48	100	5.67	104	5.50	5.75	5.75	5.75
III	12	15	7 75	1	8.00	1	5.50	1	6.25	1	6.54	100	7.17	110	6.50	7.00	6.50	7.00
IV	5	6	7 75	1	7 75	4	6.25	1	7.25	2	6.85	100	7.41	108	7.00	7.75		7.75
V	10	8	7 75	3	8.50	3	6.25	1	7.75	1	7.15	100	8.22	115	7.25	8.25	7.75	8.50
VI	8	11	7.75	3	7.75	4	6.50	3	6.75	1	7.06	100	7.41	105	7.00	7.50	7.25	7 50
VII	17	9	7 75	7	8 50	5	6.50	1	7.75	2	7.40	100	8.25	111	7.50	8.50	7.75	8.50
VIII	7	3	7.00	1	8.00	1	6.50	1	7.00	1	6.75	100	7.42	110	6.75	7.25	6.75	7.25
After 1 year		18			7 75	3			7.00	2			7.47	110		7.50		7.50
IX	5	7	6 00	1	6 75	1	5.50	1	5.50	2	5.75	100	6.04	105	5.75	6.00	5.75	6 00
After 1 year		25			6.00	5			5.50	9			5.69	99		5.75		5.75
B GASTROENTEROSTOMY. (*Pyloric Sphincter Ligated).																		
I	11	7	5.75	3	5 50	4	5 00	3	5.25	3	5 43	100	5.39	99	5.50	5.50	5 50	5 50
*II	10	4	6 00	1	7 75	4	5 00	3	7 75	4	5 48	100	7.75	141	5.50	7.25	5.75	7.25
III	1-	2	7 75	1	9 25	1	5 50	1	8 75	1	6 54	100	9.00	138	6.50	8.00	6.50	8.00
*IV	9	4	7 25	2	8 75	1	6.00	2	7.00	1	6.67	100	8.06	121	7.25	8.50	7.25	8.50
V	7	2	8 75	1	8 75	1	7 00	2	8 25	1	7.59	100	8.50	112	7.50	8.50	7.50	8.50
C PARTIAL PARASYMPATHETIC DENERVATION OF PYLORIC SPHINCTER.																		
I	18	5	6 50	1	6 50	1	5 50	3	6.25	4	5.85	100	6.30	108	5.75	6.25	5.75	6.25

the animal after operation was not suitable for further experimentation. Possibly a series might produce enough data to decide this point.

Our results on partial denervation of the pyloric sphincter failed to confirm those of Hughson (8) but were in agreement with those of Fetter, Barron and Carlson (9), and of Meek and Herrin (10). Partial parasympathetic denervation did not remove any of the food retaining function which the pyloric sphincter may normally exert. This does not mean that the vagus does not carry motor fibers to the pyloric sphincter for this has been demonstrated repeatedly by many workers. Motor fibers in the vague were also substantiated in this same animal, in another experiment, for it was shown that a particular stimulus (anoxemia, 13) caused motor activation of the pyloric sphincter before denervation and failed to afterwards. It does seem to mean that in the normal animal motor impulses do not reach the pyloric sphincter over the vagus during normal gastric emptying which by their absence after vagus section make themselves conspicuous by a decreased emptying time of the stomach. Incidentally, it is impossible to re-duplicate the results of vagus section in these experiments by atropine as we have indicated elsewhere (13).

The criticism might be made that postoperative averages are high because of the inclusion of results obtained so soon after operation that convalescent increases were still operative. This may be answered by a comparison of the high and low values before and after operation and the number of times these occurred when they were approximately equal. In addition, two animals were studied a year after operation with values only slightly, not significantly, different from those obtained during the second week after operation (see A-VIII and A-IX, Table I.).

Another possible criticism of results in this type of experiment must be mentioned. It may be that if the pyloric sphincter is effectively replaced by an unguarded exit from the stomach that materials which are usually excluded from re-entering the stomach are regurgitated. The problem then becomes, however, simply one of definition of the term "empty." We consider that this definition is not concerned with where the material may have come from, but rather with what is *in* the stomach.

Although the weight of the data presented in this paper indicates that the pyloric sphincter itself is not of very great importance in food retention in the normal stomach, this does not necessarily indicate that it is entirely without function. It may be simply another specific example of a margin of safety.

SUMMARY

Section of the pyloric sphincter (Rammstedt operation), gastro-enterostomy or partial parasympathetic denervation of the sphincter do not decrease the emptying time of the stomachs of dogs. This would seem to indicate that the normal pyloric sphincter under the influence of the stimuli effective during normal gastric evacuation, is not of appreciable value in gastric food retention.

If the pyloric sphincter itself is of value in food retention in the stomach during normal gastric evacuation, this function is taken over very quickly by some other structure after the sphincter has been sectioned, supplemented or partially parasympathetically denervated.

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Extensive Resection of the Small Intestine in the Rat with Special Reference to Anemia*

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THE relationship of anemia to abnormalities of the small intestines has been referred to frequently in the recent literature (1, 2). Any condition that interferes with the absorption of hemopoietic materials from the small intestine might lead to a deficiency type of anemia. Both macrocytic and hypochromic anemias have been observed in cases in which there is apparently a faulty intestinal absorption, e. g. coeliac disease (3); sprue (1, 4); chronic diarrhea (5); intestinal resection (1), stenosis (6), or anastomosis (4), and gastro-jejuno-colic fistula (7, 8). The simplest experimental method of mechanically decreasing the absorbing surface in the bowel is to remove a portion of it. The present study is concerned with the radical resection of the small intestine in the rat to determine further the effect of diminished intestinal absorption on hemopoiesis.

Although there are many reports in the literature of patients who have had more than two meters of small bowel removed (9), there are very few data on the

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TABLE I

Protocols on Rats Following Removal of 40 Per Cent of Jejunum and Ileum

Rat	Date	Wt. gms.	R. B. C. mill./c.mm.	Hb. gms./100 c.c.	C. I.	Remarks
202 female born 2-5-34	5-12-34	142	6.0	10.9	1.00	40 cm. jejunum-ileum removed.
	5-25	138	9.7	15.8	.80	
	6-11	171	7.8	15.0	1.06	
	6-28	183	9.3	15.8	.93	
	8-10	206	8.8	19.3	1.20	
	10-12	207				Rat healthy—sacrificed.
	2-17-35	210				No hypertrophy of bowel.
205 male born 2-5-34	5-12-34	154	5.4	10.0	1.02	40 cm. jejunum-ileum removed.
	5-25	135	9.3	13.3	.78	
	6-12	174	8.7	15.2	.95	
	6-28	205	9.6	16.2	.92	
	8-3	220	8.8	16.7	1.04	
	10-10	230				Rat sick—sacrificed, cause of death unknown.
	1-28-35	195				Slight hypertrophy of bowel.
207 female born 2-5-34	5-18-34	123	8.8	12.4	.77	40 cm. jejunum-ileum removed.
	6-4	115	7.7	13.0	.93	
	6-19	145	7.1	11.8	.91	
	8-3	170	9.4	14.7	.86	
	9-13	177	7.3	17.0	1.28	
	10-10	170				Rat healthy—sacrificed.
	2-17-35	190				No hypertrophy of bowel.
209 female born 2-5-34	5-22-34	120	10.4	12.1	.63	42 cm. jejunum-ileum removed.
	6-11	113	7.8	10.3	.72	
	6-30	144	7.3	9.3	.70	
	8-3	146	8.2	13.9	.83	
	9-13	177	8.0	14.2	.98	
	10-12	170				Rat healthy—sacrificed.
	2-17-35	180				Slight hypertrophy of bowel.
210 male born 2-5-34	5-18-34	145	6.7	11.0	.90	37 cm. jejunum-ileum removed.
	6-12	139	7.4	13.4	1.00	
	6-28	182	7.4	13.1	.97	
	8-10	209	8.0	12.7	.87	
	10-12	222				Died following removal of tumors from abdomen.
	10-18-34	238				No hypertrophy of bowel.
218 female born 2-6-34	5-12-34	126	6.1	9.9	.89	40 cm. jejunum-ileum removed followed by stitch abscess.
	6-2	121	9.1	11.8	.71	
	6-19	133	7.1	9.4	.69	
	8-3	146	9.8	17.5	.96	
	9-13	151	10.4	19.5	1.02	
	10-12	142				Died—peritonitis and obstruction. Anatomy of bowel distorted.
	10-18-34					
306 male born 1-17-34	6-2-34	147	6.2	10.3	.91	39 cm. jejunum-ileum removed. Small tumor mass in abdominal wall.
	6-18	130	6.7	10.5	.86	
	8-15	208	8.9	16.5	1.02	
	10-12	262				Rat healthy—sacrificed.
	2-17-35	322				Marked hypertrophy of bowel.

condition of the blood in this group. Becker (10) reported the case of a woman of 29 years who had over two meters of small intestine removed. Five months later, she developed a pernicious anemia blood picture and responded to liver therapy. Becker (10) quotes a case of Ryti's which also developed pernicious anemia after resection of over two meters of bowel. Saltzman (11) described the case of a woman who had 222 cm. of the jejunum removed. Four years after operation, she had pernicious anemia with achlorhydria and responded to liver therapy. Miller and Rhoads (12) stated that they removed all but a few centimeters of the ileum in dogs with the resultant production of a mild hypochromic anemia. Flint (13) found that dogs from which as much as 80 per cent of the jejunum and ileum was removed could live indefinitely but did not show a true recovery. At first, there was an excess secretion of fat and nitrogen in the feces. Gradually, the bowel hypertrophied to about twice its normal size and the nutritional balance was restored. No studies of the erythrocyte counts and blood hemoglobins are recorded.

EXPERIMENTAL

Extensive resection of the small bowel was performed in albino rats of the Wistar strain, by the method described by Jung and Jones (14) for gastrectomy in rats. This consists in the use of a magnesium cannula** over which the intestinal stumps are ligated. The cannula is completely absorbed in about two weeks. The average length of the jejunum and ileum in an adult rat was found to be about 100 cm., and of the duodenum, about 10 cm. In the first series of rats, about 40 cm. of intestine were removed beginning a few centimeters below the duodenal-jejunal flexure. In the second series, beginning at the same level, an average of 80 cm. of intestine were removed.

The age of the rats used in Series 1 was three to four and a half months and in Series 2, five and a half to seven months. In Series 1, 1 mg. iron and 0.025 mg. copper were added to the drinking water daily for two weeks preceding operation to insure an adequate storage of these minerals. The rats were kept singly in wire cages and received a stock diet of two-thirds whole wheat (containing 1% iodized sodium chloride) and one-third whole milk powder.

All rats were fasted for twenty-four hours preceding operation. The abdominal hair was removed with a solution of potassium sulphide, and operation was performed aseptically under ether anaesthesia. A 2 to 3 cm. incision was made in the midline and the small bowel was exposed. Wire clamps were placed 3 to 5 cm. below the duodenal-jejunal flexure and at about 40 cm. (or 80 cm.) below this

**The cannulae used were flanged and the dimensions were 9 mm. long and 2.5 mm. in internal diameter. Recently, Dr. Jung has found that a cannula 4 mm. long and 3 mm. in internal diameter is more satisfactory. The cannulae were purchased from V. Mueller and Co., Chicago.

TABLE II

Protocols on Rats Following Removal of 80 Per Cent of Jejunum and Ileum

Rat	Date	Wt. gms.	R. B. C. mill./c.mm.	Hb. gms./100 c.c.	C. I.	Remarks
312	11-2-34	193	8.1	14.0	.94	80 cm. jejunum-ileum removed.
male	11-23	218				
	12-7	153	7.3	13.6	1.02	
born	12-29	188	5.2	7.6	.86	
6-8-34	1-11-35	212	7.2	9.2	.70	
	2-8	241	7.1	9.8	.76	
	3-27	245	9.4	13.2	.77	
	5-7	240	8.9	14.3	.88	Skin reddish-scales on back.
	5-23-35	230				Rat in fair health—sacrificed. Marked hypertrophy of bowel.
314	11-28-34	236				80 cm. jejunum-ileum removed.
male	12-12	187	7.7	11.6	.82	
	12-29	197	3.8	6.2	.89	
born	1-11-35	197	8.1	8.8	.60	
5-3-34	2-8	240	9.7	14.2	.80	
	3-27	230	7.1	11.2	.86	
	5-8	234	9.3	12.6	.74	Skin reddish-scales on back.
	6-30	212	7.1	10.1	.78	Rat sick.
	7-3-35	198				Sacrificed—partial obstruction of bowel. Slight hypertrophy of bowel.
315	11-28-34	161				78 cm. jejunum-ileum removed.
female	12-12	142	6.1	11.4	1.03	
	12-29	165	5.4	9.6	.98	
born	1-11-35	177	6.3	9.3	.81	
5-8-34	2-8	172	7.3	12.6	.95	Placed with male, never became pregnant.
	3-27	175	8.3	10.0	.66	
	5-7	173	5.3	11.3	1.16	Skin-crusts on neck and tail.
	7-8	163	7.5	11.8	.87	
	8-16-35	144				Rat in poor health—sacrificed. Moderate hypertrophy of bowel
317	12-5-34	187				80 cm. jejunum-ileum removed.
female	12-19	178	5.6	9.5	.93	
	1-4-35	183	7.0	10.5	.82	
born	1-18	189	5.7	12.3	1.19	
4-29-34	2-18	196	9.6	16.4	.94	Placed with male 2-12-35
	3-8	214	9.3	16.4	.96	
	3-13	241	6.1	11.4	1.02	Gave birth to litter of eight 3-14-35
	4-2	178	7.8	13.2	.92	
	5-8	203	7.8	13.2	.92	Skin-crusts on neck and behind ears.
	7-8	206	10.0	16.1	.88	
	8-14-35	175				Rat sick—sacrificed—pneumonia. Slight hypertrophy of bowel
318	12-5-34	150				79 cm. jejunum-ileum removed.
female	12-19	145	9.1	12.0	.70	
	1-4-35	146	6.3	11.3	.98	
born	1-18	163	7.2	14.0	1.07	
5-8-34	2-18	165	11.1	15.2	.75	Placed with male 2-12-35.
	3-8	152	6.1	10.5	.95	5 young delivered by Cesarean at term 3-11-35.
	3-12-35					Rat died. Marked hypertrophy of bowel.
319	12-6-34	238				5 cm. jejunum-ileum removed
male	12-26	184	8.3	13.6	.85	
	1-4	178	7.7	13.0	.93	
born	1-22	235	5.7	11.9	1.16	
5-8-34	2-18	250	9.4	16.4	.95	
	3-27	250	12.1	18.0	.81	
	5-9	255	10.2	17.8	.95	Skin reddish scales on back.
	5-23-35	232				Rat in fair health—sacrificed. Marked hypertrophy of bowel

level. Bull dog clamps were placed about 1 cm. inside the wire clamps on the portion of the bowel to be removed. In Series 1, the mesentery of the bowel to be excised was included in one cat gut ligature while in series 2, two ligatures were used. The segment of small intestine was then excised and the free ends of the bowel anastomed end to end by ligation with cat gut to a magnesium cannula. The peritoneum and fascia were closed with a continuous cat gut suture and the skin with interrupted silk sutures. Following the operation, the rats were given white bread soaked with milk for two weeks, following which the stock diet was resumed.

Erythrocyte counts were performed with Bureau of Standards equipment and the blood hemoglobins with the Newcomer apparatus standardized by the oxygen capacity technique. Erythrocyte counting pipets and micro-colorimeter cups were used in the determination of the hemoglobin. Hematocrit determinations were made by the method of Rosahn (15). Blood was obtained from the tail for all determinations. The average normal erythrocyte count for rats in this colony was 8,500,000 per cu. mm. and the hemoglobin, 15.5 gms. per 100 cc. These figures were used in computing the color indexes.

RESULTS OF REMOVAL OF 40 PER CENT OF THE JEJUNUM AND ILEUM

In Series 1, 14 rats were operated, of which 7 died within a period of 21 days. The causes of death in this latter group were peritonitis, hemorrhage, lung abscess, and intestinal obstruction. These are omitted from further discussion. Of the remaining seven rats (see Table I.), No. 218 died of peritonitis after five months, No. 210 was sacrificed after the same period because of multiple abdominal tumors, and No. 205 became quite sick after 8 months and was sacrificed. The cause of its illness was not determined. Rats 202, 207, 209 and 306 remained quite normal and were all sacrificed after nine months.

The preoperative weights were reached in ten to twenty-seven days (av. 21) after operation. The animals continued to gain weight, and the maximum reached was practically that of normal adult rats in this colony. The four rats that were sacrificed nine months after operation appeared normal in every respect. There was no diarrhea in any rat in this series. During the first 1 to 2 months following opera-

tion, there was a tendency for the rats to have a mild anemia which was characterized by a color index of one or less than one. At the lowest levels, the erythrocyte counts varied from 5.4 to 7.1 million per c.mm. and the hemoglobins 9.3 to 11.8 gms. per 100 cc. The rats gradually recovered from the anemia without treatment.

At autopsy, there were always adhesions about the stoma, but no stenosis occurred in this region. In three rats, the remaining small bowel was of normal size. In two rats, there was moderate hypertrophy in localized segments of the bowel and in another rat, the remaining jejunum and ileum had hypertrophied to twice the normal size throughout. In the remaining rat, the anatomy of the bowel was distorted because of peritonitis. The term hypertrophy in the protocols indicates an increase in transverse size as determined by external macroscopic examination and the degree of hypertrophy is designated by slight, moderate, or marked. A detailed anatomical description of the remaining bowel will be the subject of another report.

RESULTS OF REMOVAL OF 80 PER CENT OF THE JEJUNUM AND ILEUM

In Series 2, 12 rats were operated, of which six died within a period of 19 days. The cause of death of rats in this latter group was infection or abscess formation about the stoma with secondary peritonitis. These are omitted from further discussion. Of the remaining six animals (see Table II.), No. 318 died 4 months after enterostomy following a Caesarian section, No. 314 died after 7 months of intestinal obstruction, and No. 317 died at 8½ months of pneumonia. Three rats (312, 319, 315), whose condition became rather poor, were sacrificed at 6, 6 and 8½ months, respectively.

It is apparent that these rats required about twice the time to regain their preoperative weight as those in Series 1. The extremes were 24 to 74 days, with an average of 44 days. After this, they continued to gain to about the same maximal levels as in Series 1. The slower gain after operation might be partly explained by the fact that the rats in Series 2 were older.

After recovery from the operation, the rats appeared to be quite normal. There was no diarrhea, but the stools seemed to be somewhat larger than normal and contained undigested food particles. About five months after operation, the surviving five rats developed skin lesions. Rats 312, 314 and 319 had reddish scaly lesions on the posterior aspect of the back, while rats 315 and 317 had crusts around the neck and back of the ears. In addition, rat 315 developed marked scaling of the tail. From this time on, all rats began to lose weight, and the skin lesions became progressively worse. Because of their downward course, the rats were sacrificed within the periods noted above. It seems questionable whether any would have survived longer than nine months. Rat 315, sacrificed at 8½ months, had severe skin lesions and showed loss of weight and marked loss of activity.

The *blood picture* varied somewhat in different rats in Series 2. Rats 312 and 314 developed a rather marked anemia which continued for a period of about eight to ten weeks following operation. At the lowest levels, the erythrocyte counts were 5.2 and 3.8 million per c.mm., and the hemoglobins 7.6 and 6.2 gms. per 100 cc., respectively. From color index and volume index determinations, the anemia in general was found to be of the hypochromic microcytic type. The blood pictures gradually improved without treatment. The remaining four rats had a less marked anemia which was similar in degree and course to that observed in Series 1. The period of decline after five months studied in several rats was not accompanied by any remarkable changes in the blood picture.

Because of the fact that Ivy, Morgan and Farrell (16) observed anemia in gastrectomized dogs during pregnancy, the effect of pregnancy was studied in these rats. About 2½ months after the bowel operations, the three males in series 2 were placed individually with females in the same series. Rat 315 never became pregnant although several normal males were used for mating. Rat 317 gave birth to a litter of eight young 4 weeks after being placed with the male. Five of these were eaten by the mother within two days, and the remainder died shortly thereafter. The blood studies in the mother were normal six days before delivery, and on the day preceding birth the erythrocyte count and hemoglobin were depressed to within the range occurring during normal pregnancy. The mother's condition seemed to be quite normal before and after the pregnancy. Rat 318, four weeks after being with the male, had a bloody vaginal discharge, was breathing rapidly and appeared quite sick. The next day, Caesarean section was performed and five full term fetuses were removed. Two of the young did not breathe, while three breathed for about fifteen minutes and then expired. The mother died the next day and at autopsy two more fetuses that were not seen at operation, were found in the opposite uterus. Blood studies three days before Caesarean section showed depression of the erythrocyte count and hemoglobin only slightly lower than the average values seen in normal pregnancy. It is thus shown that a pathologic anemia did not occur in rats with extensive resection of the small bowel when they became pregnant.

The remaining jejunum and ileum in all rats in Series 2 showed varying degrees of hypertrophy at autopsy. In all but one case, there was also hypertrophy in the duodenum. The small intestine varied from twice to four times its normal size. In some rats, there was only hypertrophy of portions of the intestines, while in others the enlargement was general throughout. As was to be expected, the hypertrophy following resection of 80 per cent of bowel was more extensive and marked than after the removal of only half as much bowel.

COMMENT

These studies show that the rat can survive when as much as 80 per cent of the jejunum and ileum is removed. Following a period of loss of weight and mild anemia, the animal improves and seems to approach a normal condition. This period of improvement is probably related to a compensatory mechanism in the remaining gut. When 40 per cent of the jejunum and ileum was removed, rats kept under observation for 9 months continued to be normal in every respect. However, when 80 per cent was removed, this was not the case. After a period of about 5 months, the rats developed skin lesions and began to lose weight. They all ran a down hill course and from this small series, it appears that they could not survive for

longer than 8 to 9 months following such an operation. The limits of safety in the removal of the small intestine from rats are thus indicated by these experiments.

The anemia which occurred during a period of one to two months following operation varied from a normochromic to a hypochromic type. This could be related to various factors such as hemorrhage (from operation), sepsis and iron deficiency from diminished absorption. The latter was probably the principle factor, especially in the production of the more severe anemia that occurred in two rats after radical enterectomy. The chronicity of the anemia and the slowness with which it improved is in favor of an iron deficiency caused by a decreased absorbing area in the small intestine.

At no time was a significant macrocytic anemia observed in these rats as shown by color and volume index determinations. If the physiology of hemopoiesis in the rat is similar to that in man, these experiments indicate that the anti-pernicious anemia principle was absorbed to a sufficient degree in the enterectomized rats to prevent the occurrence of a macrocytic anemia.

SUMMARY

1. In two series of rats, 40 per cent (Series 1) and 80 per cent (Series 2) of the jejunum and ileum were removed, respectively.

2. After recovery from the operation, rats in Series 1 remained normal over a nine month period of observation. Rats in Series 2 developed skin lesions after five months, began losing weight, and were sacrificed or died because of their declining condition within 8½ months after operation.

3. All rats developed a mild normochromic to hypochromic anemia following enterectomy while two rats in Series 2 developed rather marked hypochromic anemias. The blood picture usually recovered spontaneously within 6 to 10 weeks after operation.

4. Varying degrees of hypertrophy occurred in the remaining small intestines in all rats in Series 2. It occurred in only half the rats in Series 1 and was less marked.

The author wishes to express his appreciation to Dr. F. T. Jung for his assistance in the development of the operative technique.

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Studies on Auto-Digestion

VI. The Digestion of Living Tissues in Stomach Juice (Claude Bernard's Experiment)*†

By

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THE physiologic mechanism of the resistance offered by the stomach and the proximal intestine to digestion by their respective proteolytic ferments still remains unexplained. Some seventy-five years ago, Claude Bernard (1) repudiated John Hunter's (2) "living principle"‡ by demonstrating effectively that living tissue, as such, displayed no immunity to digestion. The immersion of living eels or frogs into the gastric juice of a dog resulted invariably in their digestion. Somewhat later, in 1863, Pavy (3) commented: "I have found that the tip of a living rabbit's ear has similarly yielded to the influence of the digestive menstrum." Subsequently observers have noted the fat necrosis resulting from acute pancreatitis as well as the severe digestion of the abdominal wall, which may appear about an inadequately constructed Pavlov pouch or gastrostomy.

In contrast to these experiments and observations, it is now generally conceded that organ or tissue implants in the stomach (4, 5, 6, 7) or duodenum (8) are thoroughly capable of withstanding the digestive milieu, providing their blood supply is adequate. Similarly negative was Ewald's (9) observation of no defection in the shaved paw of a living dog maintained for six hours in a mixture of glycerine gastric extract and HCl at body temperature.

Notably, three theories have been advanced to explain the resistance of the stomach to autodigestion. Bernard (1) ascribed the protection to the lining cells and their mucoid secretion. Since healing normally occurs rapidly if a segment of mucosa is avulsed, this assumption is now invalidated. Weinland (10) ascribed the preservation of the stomach to specific antiferments, which were also present in parasitic intestinal worms. However, previous work (11, 12, 13) in the present series of papers concluded that the existence of a specific anti-trypsin was doubtful, and similarly the possible presence of a specific anti-pepsin is questionable (14). Finally Pavy (3) "refers the immunity observed to the circulation within the walls of the organ of an alkaline current of blood." And he continues: "If the circulation through its neutralizing power protects the stomach why does it not protect the ear and the frog? The result is involved in a question of degree of power between two opposing influences and because through degree of vascularity, the neutralizing power of the circulation is sufficient to hold in check the solvent action of the gastric juice in the case of the stomach, it does not follow that it should similarly be sufficient to do so in the case of the frog's legs and the rabbit's ear. With the frog it may be fairly taken that the amount of blood possessed by the animal would be totally inadequate to furnish the required means of resistance to the influence of the acidity of a dog's gastric juice. With the rabbit's ear the vascularity is so much less than the walls of the stomach that there is nothing incomprehensible in the fact of the one yielding to and the other resisting the attack. In support of the position that has been taken, it can be shown by experiment that even with the stomach itself, by increasing the acidity of its contents beyond a certain point, its circulation is no longer adequate to enable it to resist digestion."

This theory has received some confirmation. Dragstedt and Vaughn (4) have repeated Bernard's (1) experiment and successfully digested living frogs in the gastric juice of man, dog and frog. They stress the importance of the concentration of HCl in the digestive medium, observing that the greater the concentration of acid, the greater the intensity of digestion; and that, moreover, blood vessels exhibited a greater relative resistance to peptic hydrolysis. Necheles and Fernando (1926) in unpublished experiments, made similar observations. More recently Dragstedt has reported that chronic progressive ulcers developed in experimentally isolated stomachs or Pavlov pouches (15) and that organs implanted into Pavlov pouches, with their higher unneutralized acidity are subjected to digestion (16). The presumptive importance of acidity for auto-digestion is further attested by the failure of human peptic ulcer to develop in the presence of complete anacidity (17), the not infrequent appearance of jejunal ulcers following gastro-enterostomies, the occasional development of ulcers in the ileum contiguous to a Meckel's diverticulum containing heterotopic gastric mucosa (18, 19), the diminished gastric mucus content of ulcer patients (20, 21) and the ulcer-

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‡"Animals, or parts of animals, possessed of the living principle, when taken into the stomach, are not the least affected by the powers of that viscus, so long as the animal principle remains; thence it is that we find animals of various kinds living in the stomach, or even hatched and bred there; but the moment that any of those lose the living principle, they become subject to the digestive powers of the stomach. If it were possible for a man's hand, for example, to be introduced into the stomach of a living animal, and kept there for some considerable time, it would be found, that the dissolvent powers of the stomach could have no effect upon it; but if the same hand were separated from the body, and introduced into the same stomach, we should then find that the stomach would immediately act upon it." (2).

ation yielded by the Mann-Williamson operation (22).*

Unfortunately for this theory, peptic ulcer in man may co-incide with an exceedingly low, if not negligible, acidity; and apparently may heal in the midst of high acid concentrations.

A further analysis of the problem of auto-digestion seemed warranted, and this paper represents such an attempt.

PROCEDURE

The common edible frog (Rana Esculenta) and the American bullfrog (Rana Catesbiana) were employed for this work. The digestive medium was a freshly prepared 2% solution of pepsin (Wilson & Co. 1:10,000)† in N/10 HCl.

The frogs were either pithed or narcotized with ether or urethane (2 cc. of a 10% solution injected into the dorsal lymph sac), then attached to a frog board, and the legs suspended in the artificial gastric juice contained in a beaker which was immersed in a glass constant temperature bath. In this manner, perfect visibility of the progress of digestion could be guaranteed. Unless otherwise specified, all experiments were performd at 38° C.

In one series of experiments, the abdominal aorta and the abdominal vein were cannulated and the digesting legs perfused with Ringer's solution [NaCl 0.65%, KCl 0.014%, $CaCl_2$ 0.012%, $NaHCO_3$ 0.02% (Clark, 23)]. The venous outflow was collected in a separate beaker in order to avoid dilution of the digestive fluid.

The bullfrogs were used mainly for ph determinations during the process of digestion. A modification of the non-buffer colorimetric micro-method of Hastings (24) was utilized, 2 specimens of blood, 1/10 cc. each, being collected from either the aortic arch or the abdominal vein both before and after digestion of the legs.

Throughout the entire work, comparative experiments and controls were done on the same day, using the same lot of frogs and the same sample of artificial gastric juice. The peptic activity of the digestive mixture decreased somewhat from day to day even when stored at cold temperatures. In the following tables, the serial letter accompanying the number of the experiment identifies the several tests performed under identical conditions.

Degree of digestion is expressed as definite or severe. The former denotes visible defection of the skin or superficial hemorrhage, the latter indicates corrosion of skin and musculature.

Only those experiments are reported in which cardiac activity remained unimpaired at the conclusion of the test.

RESULTS

Notwithstanding that cardiac activity was more vigorous in the etherized than in the pithed frogs, ether definitely increased the rate of digestion.

One foot of a frog was exposed to digestion; and as control, both legs of another animal were immersed in gastric juice. Pithing or anesthesia with ether or urethane were variously employed. In the four groups of pithed frogs, digestion occurred definitely sooner when a larger surface was available for proteolytic action. Similarly the urethanized frogs, in whom, as in the etherized frogs, the heart beat seemed vigorous, the rate of digestion appeared as a direct function of the exposed surface area. Contrarily, definite digestion appeared in the etherized frogs at about the same time, irrespective of the surface area exposed to digestion.

Throughout these experiments, the artificial digestion mixture was maintained at a temperature of 38 degrees C. in the constant temperature bath. The objection may be proffered that the immersion of both legs in the warm digestive medium raised the body temperature of the frog, a factor which is undoubtedly neglible if only one foot is inserted; and that the increased body temperature in the former instance may accelerate digestion. This criticism was answered by experiments 21 and 22 (Table II), which were performed at room temperature, and which entirely repeated the results obtained at the higher temperature.

Section of the sciatic nerve of the dog or cat evokes an acute acceleration of the blood flow through the extremity, an old observation recently reconfirmed by the thermo-stromuhr (25). Inferentially this should also be true for the frog. Accordingly, in etherized frogs, one leg was denervated through a small slit in the upper thigh, and then both legs were submerged to the knee in gastric juice. In all but the last test (7b),

TABLE I

Comparative Effect of Pithing and Ether Anesthesia Upon Rate of Digestion

No. of Test	Weight of Frog	Procedure	Time of Digestion in Minutes			
			Pithed		Ether	
			Definite	Severe	Definite	Severe
1a	87	Ether	22	27		
2a	63	Pithed			28	39
3b	61	Ether	21	30		
4b	44	Ether	18	26		
5b	38	Ether	11	16		
6b	42	Pithed			32	40
7b	51	Pithed			32	43
		Average	19	25	31	41

TABLE II

Relationship of the Surface Area Exposed to Digestion to the Rate of Digestion

No. of Test	Weight of Frog	Procedure	Time of Digestion in Minutes			
			One Leg Immersed		Both Legs Immersed	
			Definite	Severe	Definite	Severe
1a	40	Pithed	19	25		
2a	34	Pithed			32	40
3b		Pithed	20	22		
4b		Pithed			38	47
5b		Pithed			33	46
6c	50	Pithed			34	40
7c	55	Pithed	17	24		
8c	51	Pithed	24	29		
9d	47	Pithed	20	32		
10d	51	Pithed			43	52
		Average	20	27	37	45
11c	52	Ether			43	50
12c	34	Ether			29	36
13c	27	Ether			36	46
14c	24	Ether	16	18		
15c	29	Ether	12	30		
16c	30	Ether	14	29		
		Average	14	26	35	44
17d	54	Urethane			39	46
18d	39	Urethane	41		45	51
19d	50	Urethane	very slight	—		
20d	56	Urethane	40	65		
		Average	41	65	43	49
21c‡	46	Urethane	No digestion after 42 minutes		42	59
22c	74	Urethane				

Test 21 and 22 were done at room temperature (24° C.).

*It is to be recognized that observations are available which show that true, chronic peptic ulcer can develop in the presence of anacidity. Similarly, gastrojejunal ulcer has been reported in humans whose stomachs were acid free. *Editor.*

†We acknowledge our indebtedness to Dr. D. Klein of the Wilson Laboratories for his contribution of pepsin.

the denervated leg was digested more rapidly than the normal control.

In this same group belong another series of experiments, which have not been tabulated. Ergotamine tartrate (½-1 mg.) was injected into frogs in an effort to paralyze the sympathetic nerve supply and thereby prevent vaso-constriction in the digesting legs. The results, however, were inconstant.

TABLE III

Influence of Denervation Upon the Rate of Digestion

No. of Test	Weight of Frog	Time of Digestion in Minutes			
		Sciatic Cut		Control Leg	
		Severe	Definite	Definite	Severe
1a	21	4	14	0×	0×
2a	20	15	18	15	0××
3b	95	22	25	0+	0+
4b	40	15	26	18	40
5b	35	14	20	20	0××
6b	38	13	18	19	26
7b	25	15	18	15	18
	Average	14	20	(12)	(12)

×No digestion after 14 minutes.
××No severe digestion after 20 minutes.
+No digestion after 25 minutes
Ether anesthesia. In 1a the left, in the rest of the experiments the right sciatic was cut.

Dragstedt and Vaughn (4) reported that a higher concentration of HCl in gastric juice accelerated digestion of living frog legs. Since such procedure introduced a somewhat unphysiologic element, a different approach was attempted in the present work. In this series of experiments, one leg of a frog was dipped in gastric juice and the other exposed to air, Ringer's solution, alkali (isotonic) or N/10 HCl.

It will be observed that HCl produced the most rapid digestion of the opposite leg immersed in gastric juice and alkali the slowest digestion, the experiments in air and Ringer's solution occupying an intermediary position.

With the exception of experiments 6c and 7c, the perfused legs were digested slower than the legs of control pithed frogs.

The remainder of the experiments in this group is devoted to a study of the comparative influence of perfusion with Ringer's solution with and without bicarbonate. The absence of bicarbonate tended to hasten digestion.

Experiments on Bullfrogs. The rate of digestion of bullfrog legs did not vary significantly from that observed in the small frogs.

In the course of digestion, a number of pH determinations were made upon blood taken from the aorta and abdominal vein, but the results were inconclusive. A drop of pH from 7.35 to 7.30 was observed in one blood specimen taken from the abdominal vein when digestion of the legs had set in. Similarly, a drop from 7.4 to 7.35 was noted in the blood of another animal. However, in other tests, no change in pH was observed, although severe digestion occurred.

In order to test the protective influence against digestion of the skin mucus of frogs, pilocarpine hydrochloride (1-4 mgs.) was injected into the lymph sac of frogs, and their legs submerged in gastric juice. Control frogs were simultaneously exposed to digestion. In only one frog (rana esculenta) did a visibly increased secretion of mucus develop on the skin in response to the pilocarpine, and in this frog digestion was considerably delayed. In other frogs, no significant difference could be detected between control and pilocarpinized animals. Likewise, injection of calcium gluconate did not alter the digestion time.

DISCUSSION

The data presented above can be conveniently grouped into two major categories. The first group includes those experiments which may possibly express the effect of local changes upon the rate of digestion. The second rubric comprises those experiments providing some insight into the systemic response to digestion of a living anesthetised frog.

Apparently ether exercises a deleterious action on the tissues of the frog, rendering them more susceptible to digestion. Although the circulation is certainly better in the etherized than in the pithed frogs, the former are the more rapidly digested. Significantly, the frogs anesthetized with urethane, whose circulation was entirely comparable with that of the frogs narcotized with ether, manifested a slower rate of digestion than the etherized frogs. Thus the conclusion seems justified that ether, in some way, peculiarly predisposes frog legs to digestion.

Further, it is quite as difficult to explain the more rapid digestion of a denervated leg. Actually one might expect the converse, that section of the sciatic nerve, which probably increases the blood supply to the leg of the frog, would increase the resistance of the extremity to digestion. It may, of course, be possible

TABLE IV

Effect Upon the Rate of Digestion of One Leg Immersed in Gastric Juice When the Other Leg is Simultaneously Exposed to Air, Ringer's Solution, Alkali, or Acid

No. of Test	Weight of Frog	Digestion Time of Right Leg (in minutes) when Left Leg was Exposed to:							
		Air		Ringer		Alkali		Acid	
		Definite	Severe	Definite	Severe	Definite	Severe	Definite	Severe
1a	45	18	55						
2a	38		65						
3a	40					65+			
4a	42					—×	—		
5a	39					—××	—		
6b	43			35	40				
7b	35			32	37				
8b	55			31	40				
9b	42							30	—[c]
10b	42							16	33
11b	40							22	29
12b	44							24	30

Urethane Anesthesia.
No digestion after 55 minutes.
No digestion after 60 minutes.
No severe digestion after 35 minutes.
—Very slight.

TABLE V

Influence of Perfusion Upon Rate of Digestion

No. of Test	Time of Digestion in Minutes			
	Perfused Frog		Pithed Frog	
	Definite	Severe	Definite	Severe
1a	85			
2a				60
3b		90		
4b				60
5c	60			
6c	60			
7c			60	
8c				60
9d	—×	—		
10d	—×	—		
11e			60	
12e			60	
	PERFUSED FROGS			
	Ringer		Ringer without Bicarbon	
	Definite	Severe	Definite	Severe
13f			60	
14f	—××			
15g		—+	60	120
16g	60	—+		
17h	60			
18h			60	

×No digestion after 60 minutes.
××No digestion after 70 minutes.
+No severe digestion after 120 minutes.

that this interpretation is wrong, and that instead acute stasis results from denervation.

Perhaps the explanation for the rapid digestion induced by ether or denervation will be discovered ultimately in an increased permeability of the tissues to the digestive milieu.

Evidently the digestion of living frog legs is not merely a local phenomenon of the acid destroying the cells, which, when dead, are readily digestible. Instead, the rate of digestion is distinctly related to the surface area exposed to the gastric juice (Table II). The greater the available surface, the sooner the first signs of digestion appear. It is possible, although not probable, that the blood may contain some protective substances, whose rate of exhaustion is dependent upon the surface area immersed in the digestive medium. More likely as explanation for this phenomenon is the possibility that, although no significant change in blood pH occurs with digestion, the alkali reserve is none-the-less diminished considerably. The experiments listed in Table IV tend to substantiate this interpretation, for the immersion of one leg in isotonic alkali solution delayed digestion of the opposite extremity. The slower digestion in the perfusion experiments and the suggestive evidence contained there that bicarbonate may modify the digestion rate is also partly confirmatory. However, a number of tests in which alkali or acid was injected into the lymph sac and digestion time of the legs determined yielded inconstant results.

Two possibilities are available to account for the loss of base which may occur in the process of digestion. *Acid may be absorbed, uniting with the blood* base to form neutral salts. Or again, the gastric juice may alter the permeability of the frog's skin, which normally resists the passage of ions to the exterior, and in this manner permit an escape of base. Since calcium injections did not increase the frog's resistance to digestion, the possible loss of this important ion as a factor in digestion is ruled out.

SUMMARY

Legs of frogs anesthetised with ether are digested more rapidly by stomach juice than those of pithed frogs, or of frogs anesthetised with urethane.

Legs of frogs in whom the sciatic nerve is cut are digested more rapidly than innervated legs.

The larger the surface area of the frog's legs immersed in gastric juice, the sooner will appear the first signs of digestion.

It is concluded that digestion in this experiment is not due merely to a local process, but possibly results from alkali depletion of the blood.

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SECTION III—*Nutrition*

A Survey of Four Hundred Ninety Diabetic Admissions to General Hospitals

By

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THAT diabetes and its associated complications continue to be a significant cause of physical incapacity and death, is fairly common knowledge. That this should be true in light of the present knowledge of the control of the disease has led to the author's study. We wished to observe just what the status of the diabetic patient might be in a community where the general hospitals are well equipped but have no specific diabetic service, and where the general practitioners care for more of the diabetic populace than internists who would like to emphasize diabetes.

From 1929 to 1934, inclusive, there were 490 admissions of diabetic patients to four general hospitals in Dallas, Texas. When 53 re-admissions are subtracted there were, for that period, a total of 437 patients. Of the admissions there were 223 males, or 45.5 per cent, and 267 females, or 54.4 per cent. The age distribution by decades is as follows:

TABLE I
Age Distribution by Decades

Decades	1st	2nd	3rd	4th	5th	6th	7th	8th	9th
Males	7	17	30	30	35	44	38	20	1
Females	6	21	23	34	41	60	53	20	0
Total	13	38	53	64	76	104	91	40	1
Per cent	2.7	8.0	11	13.4	15.8	21.7	19.0	8.4	

(The above includes 480 patients. Ages of 10 patients were not recorded).

It is to be noted that there is a slight preponderance of males in the third decade group and a preponderance of females in the sixth and seventh decades (Fig. 1). The model class for both sexes is the sixth decade. Murray-Lyon (1), in an analysis of 1700 cases, likewise found that relatively more males developed diabetes before the age of 40 years. (37.9 per cent of men and only 19.9 per cent of women developed the disease before this age). Authors seem fairly well agreed that women are more susceptible to diabetes than men. Murray-Lyon found 64.5 per cent of his group to be women.

In the present series the date of onset of symptoms could be fairly well determined in 347 patients. There were but 83 patients (24 per cent) of this group who entered the hospital for the first time within 5½ months of the beginning of their illness and there were 86 patients (25 per cent) who had symptoms of diabetes for 5½ years or longer before their first hospital admission. The average duration of symptoms before the first admission was 42 months (3½ years). The average loss of weight in the patients before admission was 31 pounds.

There were 81 deaths of the following causes:

TABLE II
Diabetic Deaths

Cause of death	Number of deaths	Per cent
Coma	31	38.3
Cardiovascular-renal (uremia-gangrene)	25	30.9
Septicemia	12	14.8
Pneumonia	8	9.9
Skull fracture	2	2.4
Strangulated hernia, carcinoma and undiagnosed	1 each	

COMA

There were 62 patients admitted in varying stages of coma with a mortality of exactly 50 per cent. In the group of 31 deaths from coma there were 22 patients who died in less than 48 hours after admission to the hospital. This group of moribund patients actually averaged but 17 hours in the hospital before death. The remaining nine patients from the group dying in coma were in the hospital from 53 hours to 5 days. Thirteen of the group were males and eighteen were females.

Flynn (2), in 43 diabetic deaths, (Peter Bent Brigham Hospital, 1923-1933) found only 5 per cent due to coma; 49 per cent, cardiovascular-renal; 28 per cent, sepsis; 7 per cent, pulmonary tuberculosis; and 11 per cent, unusual complications. The Metropolitan Life statistics show coma as the cause of death in 37 per cent of the total fatal cases of diabetes for 1930 (3). In New York City for the same year, Bolduan (4) re-

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ported 23 per cent of diabetic deaths as due to coma. In the New England Deaconess Hospital (5) from May, 1923, to October, 1934, coma deaths constituted but 11.4 per cent of the total deaths. Of 276 coma admissions there were 35 deaths (12.7 per cent).

It seems obvious that carelessness and ignorance on the part of the diabetic patients, negligence and incompetence on the part of many physicians treating diabetes, and certain, as yet, uncontrollable factors in diabetic coma (notably shock and hyperpyrexia) (6) are responsible for the high mortality in this group. The great majority of diabetic patients scattered over the continent are not benefiting by the accumulated medical knowledge of the prevention and treatment of diabetic acidosis.

GANGRENE

In the present series seventy-three (15 per cent) of the patients admitted with diabetes had gangrene as a complication. The average age for gangrene in the charity hospital group (42 patients) was 52.2 years; the average for gangrene in the private hospital group (31 patients) was 59 years; the average for the total, 55.3 years. In the total group there was record of an amputation in 16 patients with 7 deaths soon after amputation. In the total group of 73 there were 21 deaths, a hospital mortality of 29 per cent in patients with gangrene.

In those patients with gangrene where the duration of symptoms was recorded, an average of 7½ years elapsed between onset of the illness and admission to a hospital. There were 37 males and 36 females with gangrene of one or both lower extremities. The information available in the series does not warrant separation of the group into "arteriosclerotic gangrene" and "diabetic gangrene" by the criteria of Kramer (7). Kramer reviewed the incidence of gangrene from twelve hospital series and found it to vary from 3.2 per cent at the University Hospital, Michigan, to 18.0 per cent in the Charity Hospital, New Orleans, in the period 1921-1926. The average for the group was 6.28 per cent. Kramer's 58 cases constituted but 5.75 per cent of his own group of diabetic patients. Strauss (8), in the Jewish Hospital in Berlin, found gangrene of the extremities in 7 per cent of men and 5 per cent of women. Vale (9) found gangrene in 6.9 per cent of diabetic admissions. Eliason and Wright (10) found that 104 (16 per cent) of 652 patients had gangrene and had an immediate operative mortality of but 3 per cent though there was a follow-up mortality of 61.1 per cent in twelve months. Dillon and Hitzrot (11) had 29 (4 per cent) patients with gangrene in 725 diabetic admissions. Murphy and Moxon (12) found 72 (8.7 per cent) patients with gangrene in the Milwaukee County series (from 1922-1930) of 827 patients. Sevringhaus (13) had 50 (10 per cent) cases of gangrene in 500 patients.

In the Dallas series it is found that 27 patients (34 per cent) of the group with gangrene are less than 51 years of age. This gives an average age for gangrene in hospital admissions comparable to the average age in an era before the use of insulin (10). In fact, only a minority of the group of patients with gangrene gave a history of the use of insulin before appearing at the hospital.

The 25 patients dying a cardiovascular-renal death, including uremia and gangrene, were all over forty years of age, fifteen of them being in the seventh and eighth decades. The average age for the group was slightly above sixty years.

OTHER COMPLICATIONS

Of the complications presented by the patients in the present series, arteriosclerosis, as would be expected, leads. (Table III). Its mention occurs in 181

TABLE III

Complications of Diabetes Mellitus

Complications	Number of patients	Per cent
Arteriosclerosis	181	37
Gangrene	73	15
Coma (including semi- or pre-coma)	62	13
Furuncle, abscess or carbuncle	48	10
"Diabetic neuritis"	40	8.2
Syphilis	25	5
Cataract	17	3.5
Tuberculosis	10	2.0
Psychosis	8	1.6

(37 per cent) of the clinical records and we may presume that the figures should be even higher. Its significance is appreciated by a reference to the causes of death in any group of diabetic patients.

There were 40 patients (8.2 per cent) with symptoms of diabetic neuritis. This, again, is a finding not carefully sought for in the hospital histories. Murray-Lyon (1) found neuritis in 24.6 per cent of his patients and Sevringhaus (13) found it present 36 per cent of the time.

A positive Wassermann occurred in 25 (5 per cent) patients, most of them having latent syphilis, i. e., without clinical evidence of the disease. Lemann (14), in 1929, found 3.6 per cent diabetic patients with syphilis and concluded that there was little ground for an assumption of a causal relationship between the venereal infection and the failure of the carbohydrate metabolism. Brandau (15) reported a case of the combined disease in 1930 where anti-syphilitic treatment brought an improvement in the carbohydrate tolerance. He felt that such a relationship must be rare.

Root (16) has treated thoroughly of the relationship of tuberculosis to diabetes. He found 101 patients (6.7 per cent) in a group of 1503 fatal cases of diabetes to have tuberculosis. The Dallas series has a record of pulmonary tuberculosis in ten patients (2 per cent). Fitz (17) found 35 cases (2.3 per cent) of tuberculosis among 1529 diabetic patients. Lyon (18)

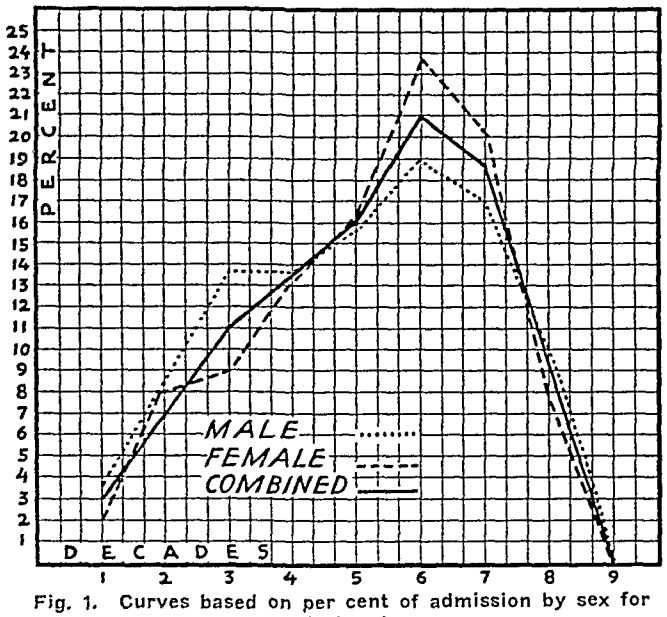


Fig. 1. Curves based on per cent of admission by sex for each decade.

reported 11 deaths (7.3 per cent) from tuberculosis in 150 diabetic fatalities in England. Among 6000 of Joslin's (19) patients there were 127 patients (2.1 per cent) with tuberculosis. Murphy and Moxon (12) had 40 cases (4.83 per cent) in the analysis of records of 827 diabetic patients. Flynn (2) found tuberculosis one of the four common causes of death in diabetes mellitus. He reported that in a group of 43 hospital diabetic deaths, with autopsy, in the past eleven years, tuberculosis caused the death in 3 patients (7 per cent). In contrast, Sevringhaus (13) considered tuberculosis infrequent, having found but 3 deaths from that cause in 500 patients.

HEREDITY

Forty-five patients gave a family history (implying only parents, brothers and sisters) of diabetes, an incidence of slightly more than 10 per cent (discounting re-admissions). This figure would undoubtedly be higher if the family histories had been more carefully recorded and had included information concerning grand-parents, siblings, cousins, etc. Sevringhaus (13) obtained a family history of diabetes in 102 patients (20.4 per cent) of his group. Strauss (8) noted hereditary influences in 20.6 per cent of the women and 29.7 per cent of the men in the Jewish Hospital in Berlin. Cammidge (20), in 1934, published the high incidence of 396 (39.6 per cent) in 1000 diabetic patients with a familial history of the disease. There were 50 patients (10 per cent) in a control group of 500 non-diabetic histories with diabetes in some member of the family. Wright (21) carefully reviewed the topic and reported the findings of twenty-one authors between 1878 and 1928. The family incidence varied from 5.3 per cent to 43 per cent with an average of 20.5 per cent. Maddox and Scott (22) emphasized the need for care in recording the family history and in considering all blood relatives. They found that the family incidence can be determined in one-third (34 per cent) of the patients with diabetes mellitus and in 10.8 per cent of non-diabetic patients.

RACE

Of the diabetic admissions, there were 18 colored males and 26 colored females (an incidence for the negro race of 9 per cent). This group had a relatively higher proportion of complications, especially gangrene, than was observed in the white diabetic patients. Otherwise we find, as did Leopold (23), that diabetes in negroes differs in no notable character from the disease in the white race. Leopold found that the negroes formed 28.8 per cent of the new admissions to the Diabetic Clinic in Baltimore. Syphilis seemed not to play an etiologic rôle in the colored race.

PREVIOUS TREATMENT

It was observed that but one-third of the patients in the present series had made the slightest effort to control their disease before admission to a hospital, in spite of the fact that the average duration of diabetic symptoms had been 3½ years. Eisenbud (24) has been impressed with the small fraction of diabetic patients receiving proper care. In 195 patients with diabetes admitted to Harlem Hospital from 1930 to 1932, he found that only 6 had received proper care prior to admission.

SUMMARY AND CONCLUSIONS

1. A survey of 490 diabetic admissions to four general hospitals in Dallas, Texas, shows the disease well distributed in all decades of life, with the greatest number of admissions in the sixth decade and with slightly more females (54.5 per cent) affected than males. Before the age of forty, diabetes occurred more frequently in males.

2. In considering the duration of symptoms before the first hospital admission the median was found to be 42 months (3½ years) and the quartiles, 5½ months and 66 months (5½ years) respectively.

3. Of the total admissions there were 81 deaths (16.6 per cent) in the hospital. Coma, the availability of insulin notwithstanding, was the chief cause of death (38.3 per cent of the fatal cases) in the period 1928 to 1934. Cardiovascular-renal complications led to death in 30.9 per cent and septicemia in 14.8 per cent.

4. One-half of a total of 62 coma patients died in coma. Twenty-two of these were admitted as moribund patients and died within a few hours. Of 39 patients less than 40 years of age with coma, 16 (41 per cent) did not survive.

5. Seventy-three (15 per cent) of the admissions had gangrene of one or more of the extremities and at the average age of 55 years.

6. No attempt has been made to analyze the factors responsible for the continued seriousness of diabetes mellitus, a controllable disease, as a social and medical responsibility. No separate diabetic service is maintained in any of the four hospitals furnishing this series. It is felt that the facilities offered for the

treatment in this group are on a par with a cross-section of the facilities in the nation at large. In an attempt to obtain better management of diabetes in this locality, the author, in 1934, began an out-patient clinic in co-operation with the City-County Hospital to afford frequent consultation and careful education of indigent diabetic patients both prior to and after hospital admissions. Some means must be found to lessen the disparity between the available scientific knowledge of the disease and the present application of that knowledge to the vast majority of patients.

Acknowledgement

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SECTION IV—*Roentgenology*

Radiological Demonstration of an Allergic Reaction in the Mucosa and Musculature of the Colon

By

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DISTURBANCE in the muscular tone of the colon after the ingestion of a specific symptom producing food was first described by Eyermann (1). He was able to reproduce the original pain by the purposeful inclusion of wheat in a wheat sensitive patient's diet, and during this experiment, by palpation of the colon at frequent intervals, observed an increasing spasticity and tenderness throughout its entire length. A film of a barium enema taken during a period when pain was not present showed a normal haustration with a tendency to hypotonicity in the ascending portion of the colon. A later film was made while there was subjective pain present due to the feeding of wheat and showed a "disharmonic colon, hypotonic in the caecum and ascending portion and hypertonic in the transverse and pelvic portions. The haustra are small, distinct and well separated." Symptoms were relieved at this time by the administration of adrenalin. Rowe (2) was able to demonstrate gastric retention arising from pylorospasm due to food allergy and to produce hypermotility and colonic spasticity after the purposeful feeding of known allergene in patients whose previous radiological studies while on compatible diets were distinctly normal. Andresen (3) has recently called attention to the marked variation in radiographic findings at interval observations which he attributes to muscle spasm and to edema of the gastric and intestinal mucosa, due to allergic reactions. Morris (4) demonstrated edema in a piece of gastric mucosa recovered during the process of lavage in a patient with generalized angio-edema and with

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Fig. 1. Taken during the attack of pain showing incomplete canalization, marked spasticity of the colon, intolerance of the splenic flexure of the colon to barium with distinct visualization of this portion of the colon due to thickening from edema and the shadowy outlines of the partially filled haustral forms of the mid portion of the transverse colon from the same cause. Note difference between the mucosal edema and gas in other portions of the film.

gastro-intestinal symptoms. Christian (5) recounts the experience of a patient with obstructive symptoms who had a sausage like shadow in an upper loop of the ilium which disappeared spontaneously. As the patient had previously developed urticaria and purpura, and as both of these conditions are now known to be allergic possibilities, it is quite likely that this was a demonstration of edema of the intestinal mucosa. Radiographic demonstration of edema of the intestinal tract is difficult as the condition tends to be transitory and frequently the patient is too acutely ill to be subjected to manipulation. In the following case edema and spasm of the colon was visualized quite by accident.

Mr C B., aged forty, was seen in consultation on January 9, 1934. He had been perfectly well until about ten a.m. on the preceding day when he began to have an agonizing pain in the lower abdomen which increased in severity and produced a desire to defacate. He had a normal bowel movement but no relief from pain. By midafternoon the pain had increased in severity and he called to see his physician who gave him some powders to take. The medication had no effect other than to produce nausea. Because of nausea no food was taken at the usual dinner time and at eight o'clock he vomited some mucus. As the pain continued he called his physician who told him that he had a temperature of 102° and gave him a hypodermic injection to ease the pain. He was able to sleep a short while but was awakened in the early morning by pain. Later in the morning he had a temperature of 101°, and as the leukocyte count had been found to be 17,000, his physician advised hospitalization and an exploratory operation. The patient consented to go to a hospital but requested a consultation before he was willing to submit to an operation. At five p.m. when seen by me the patient was evidently in great pain but he did not look toxic. He described his pain as constant with acute exacerbations starting in the umbilical region, gradually increasing in severity to a peak, then being referred down the left side of the abdomen and slowly being partially relieved. There had been no bowel movement since the preceding day but small amounts of flatus had been passed. The abdomen was greatly distended throughout and perfectly rigid There was marked tenderness in the right and left lower quadrants. Deep palpation in either region reproduced the cyclic pain. The pelvic colon was palpable, spastic and exquisitely tender. By following the course of the descending colon up the left side of the abdomen to the splenic flexure and exerting pressure it was found that the cyclic pain could be reproduced. The transverse colon could not be palpated owing to muscle rigidity. It was noted that the patient had a very marked tache cerebrale. His temperature was 100.4, pulse 96 and the leukocyte count was 12,500 In order to rule out an intestinal obstruction an open roentgen film of his abdomen was taken and found to be negative except for much gas. To eliminate diverticulitis of the sigmoid a barium enema was suggested and the colon as far as the distal half of the transverse colon was slowly and painfully canalized. The film of the opaque enema showed a very spastic colon but no other abnormalities that were recognized at the time. On close re-questioning the patient from the standpoint of a possible food sensitization which



Fig. 2. Barium enema taken four weeks after the attack of pain showing complete canalization of the colon

was suggested by the markedly hyperactive skin, it then developed that there had been a very severe attack of urticaria six years previously from bananas, and that nausea, vomiting and diarrhea had occurred in childhood and in early adult life whenever he ate pork. After abstaining from pork for fifteen or twenty years, he had eaten a large quantity of fresh pork sausage on the evening preceding the attack. There was a strongly positive allergic history in two sisters but none in any other members of his family. Adrenalin as a method of specific therapy was objected to by the family physician so morphine gr.¼ and atropine sulphate gr.1/100 was given. This was considered to be a safe procedure as the temperature and leukocyte count were lower than the earlier determinations and also because it was felt that the condition was of an allergic nature. The patient was seen the following morning and though greatly improved still had the recurring cycles of pain in a less degree. As rigidity had disappeared the entire colon could be palpated and was tender throughout its course. A proctoscopic examination was made. The mucosa of the rectum and pelvic colon was a shiny red and coated with a glistening mucosa. There were no ulcerations or points of hemorrhage. The stained smears of the mucus contained large numbers of eosinophiles. Adrenalin was again advised, it was given and relief from pain was experienced as a result. The patient made an uneventful recovery. Since that time he has experienced a similar but much less severe attack from eating baked beans cooked with pork.

Though it was established later by test, by passive transfer and by trial diet that this condition was due to a food sensitization, and it was recognized that the marked spasticity and tenderness of the colon was an allergic manifestation, the edema of the mucosa was not recognized as such until long after this case had been included in a report on "The Acute Allergic Abdomen" (6).

By comparing the radiograph shown in Figure 1, which was taken during the attack of acute pain, with the one taken four weeks later, it will be seen that there is a shadowy outline of the bowel in the more distal portion of the transverse colon as it approaches the splenic flexure and that the barium filled haustral forms are outlined in a similar fashion. These shadows are interpreted as being edema of the mucosa of the colon and it will be seen that they are quite distinct in appearance from the shadows of colonic and intestinal gas which can be seen in other portions of the film. Furthermore no such shadows are to be observed in the radiograph which was taken later.

The clinical picture as presented here was considered to be one of an acute gastro-intestinal allergy rather than a peritonitis for numerous reasons. The patient appeared to be in pain but he did not look toxic. The marked tache cerebrale, the past history of allergic episodes, the ingestion of a large quantity of a previously known offending food before the onset of pain, together with the history of two sisters being markedly food sensitive was presumptive evidence of an allergic reaction. This was later borne out by the finding of large numbers of eosinophiles in the mucus obtained through the proctoscope, by passive transfer of sensitivity and finally by the reproduction of identical symptoms by the specific feeding of pork. It is known that temperature reactions of varying degrees can accompany an allergic reaction (7). It is also known from leukopenic index studies that the ingestion of a food capable of producing a profound systemic shock is followed by an immediate leukopenia which in turn is frequently followed by a hyperleukocytosis which persists until food is taken again (8).

It is felt that the film of a barium enema taken during an attack of acute abdominal pain demonstrates an allergic reaction in the mucosa as well as in the muscular layers of the colon.

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SECTION V—*Therapeutics*

Phenolpthalein Administration to Nursing Women*

By

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THE question as to which cathartics are excreted in the milk of nursing women to a sufficient extent to affect the babe has, it seems, not been so extensively studied as the importance of the subject would justify.

Kwit and Hatcher (1) have investigated the excretion of phenolphthalein in five women who were given a single dose of from 0.03 to 0.09 Gm. of phenolphthalein and had milk drawn after intervals of six, twelve, and eighteen hours. Not one of the fifteen specimens of milk afforded a pink color after the addition of sodium hydroxide, by means of which it is possible to detect as little as 0.03 mgm.-%. They conclude that a quantity of phenolphthalein below this percentage could not exert any perceptible action on a normal infant.

AUTHORS' STUDY

In view of the practical importance of the question, it seemed desirable to repeat Kwit and Hatcher's study with certain modifications of technic in order to make the results even more conclusive, if possible. We, therefore, administered to nursing women phenolphthalein in doses ranging from 0.20 to 0.80 Gm: doses which we found these nursing women tolerated very well and in quite a proportion of cases without any resulting bowel movement.

"Yellow phenolphthalein," a product developing in the course of the manufacture of phenolphthalein and differing from the U.S.P. product in color and also with respect to certain as yet unidentified principles which it carries, has come into considerable use, as it seems to have a higher degree of cathartic action. Because of the interest which this use has created and also because even the 0.80 Gm. dose of U.S.P. phenolphthalein was not uniformly effective in securing bowel evacuation in these bed patients, we gave to another group of women this "yellow phenolphthalein" in doses of 0.30 Gm. to 0.40 Gm., which, as will be seen from the record (Table II), was quite consistent in producing bowel evacuation: the dose of 0.30 Gm. was generally sufficient.

METHOD OF STUDY

Either form of phenolphthalein was administered in form of the powder packed into capsules.

A small quantity of milk was drawn alternately from the right and the left breast of women who had been given phenolphthalein 3 or 4 hours previously. The milk was drawn in most cases both before and after nursing the babe; and, only when it became evident that there was no difference in the specimens drawn at these two times,

TABLE I

Effect of Phenolphthalein (U.S.P.) Upon Nursing Women and Their Babes

Date	Name	Dose	Effect on Mother		Effect on Baby	Free Phtn.	Conj. Phtn.
		Gm.	B. M.	Cramps	Diarrhea		
11/3	E. S.	0.20	0	0	0	0	0.04mg-%
11/6	C. W.	0.40	0	0	0	0	0.05mg-%
11/8	H. D.	0.60	++	+++	0	0	0.05mg-%
11/10	L. N.	0.60	0	0	0	0	0.075mg-%
11/12	A. P.	0.80	0	0	0	0	0.10mg-%
11/13	L. R.	0.80	++	0	0	0	0.03mg-%
11/14	C. C.	0.60	+	0	0	0	0.05mg-%

was the securing of a specimen before feeding abandoned. The study was continued for twenty-four or more hours after the giving of the dose.

The effect on the mother's and the baby's bowel movements was carefully observed and recorded.

Free phenolphthalein was searched for by the addition of N/10 sodium hydroxide V. S. to the milk. By means of this test it is possible, as stated before, to determine by the development of a distinct pink tint, the presence of as little phenolphthalein as 1 part in 3,000,000.

Conjugated phenolphthalein was searched for because it is known that a portion of the phenolphthalein that is absorbed is "conjugated," probably in the liver, by combination with certain other as yet unknown bodies. In the case of the simpler phenols, it is known that sulphate and glycuronate combinations are formed, and that such conjugation results in bodies that are largely inert biologically and that do not have the characteristic physical or chemic properties of the original substance. The determination of

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TABLE II

Effect of Yellow Phenolphthalein Upon Nursing Women and Their Babes

Date	Name	Dose	Effect on Mother		Effect on Baby	Free Phtn.	Conj. Phtn.
		Gm.	B. M.	Cramps	Diarrhea		
11/15	E. C.	0.30	0	0	0	0	0
11/17	M. F.	0.40	0	0	0	0	0
11/18	G. W.	0.40	++	0	0	0	0.10mg-%
11/19	M. S.	0.40	++	0	0	0	0.10mg-%
11/21	R. B.	0.30	+++++	0	0	0	0.05mg-%
11/22	M. L.	0.30	+	0	0	0	0.05mg-%
11/24	K. F.	0.30	+	0	0	0	0.05mg-%
11/25	J. C.	0.30	+++	0	0	0	0.05mg-%
11/26	R. L.	0.30	++	0	0	0	0.05mg-%
11/27	K. E.	0.30	+++	0	0	0	0
11/29	B. Q.	0.30	+	0	0	0	0
11/30	L. C.	0.30	+	0	0	0	0
12/2	M. B.	0.30	++++	0	0	0	0
12/3	E. H.	0.30	++	0	0	0	0.03mg-%
12/4	L. B.	0.30	++	0	0	0	0

conjugated phenolphthalein in the milk was carried on by the following process: 5 c.c. of milk and 5 c.c. of 10% hydrochloric acid were heated on a water bath for two hours. This mixture was then transferred to a separatorly funnel and shaken out with several portions of ether. The assembled ether fractions were then shaken out with N/10 NaOH V. S.; and the amount of phenolphthalein was calculated colorimetrically.

RESULTS

It was thought best not to burden this article with a detailed report of the case studies, but merely to present in tabulated form a summary of the data secured from this investigation which included the analysis of 165 specimens of milk for free phenolphthalein and 31 tests for conjugated phenolphthalein.

Table I shows the results secured from various doses of U.S.P. phenolphthalein. Table II gives the results obtained with yellow phenolphthalein. Our results agree with those of Kwit and Hatcher in that, even with the large doses employed, *there was no free phenolphthalein in any of the milk specimens tested*, at least as far as the limits of accuracy of this test are concerned. The correctness of these results is also borne out by the fact that *none of the babies developed any diarrheal tendencies from the taking of this milk.*

We find conjugated phenolphthalein present in all the specimens secured after the administration of white phenolphthalein and 55.5 per cent of the cases of yellow phenolphthalein administration, and absent in the remainder. The obvious idea that conjugated phenolphthalein, the result of absorption, is most likely to be found the longer the phenolphthalein stays in the bowel, in other words when there is no laxative action, is not entirely borne out by our results. The quantity of conjugated phenolphthalein found in all specimens is extremely minute, ranging from 0.05 mgm.-% to 0.1 mgm.-%, with the majority at 0.05 mgm.-%. This means that there is at most 1 part in 1,000,000 and that generally it is only one-half or one-third as much. From our results we can definitely say that *conjugated phenolphthalein in these quantities is not laxative to the babe.*

CONCLUSIONS

1. No free phenolphthalein is excreted in the milk of nursing women in the course of twenty-four hours or more after the taking of large and liberal doses of phenolphthalein: of the U.S.P. as well as of the yellow variety.

2. Minute quantities of conjugated phenolphthalein are present in the large majority of all specimens of the milk of nursing women taking phenolphthalein.

3. There is no obvious effect upon the bowel movements of the babe nursed by a woman who has taken phenolphthalein.

4. Our results indicate that the yellow phenolphthalein is more active as a laxative in the bed patients studied than the U.S.P. product.*

*Our thanks are due to Dr. David S. Hills for permission to conduct this study upon his cases, and to Dr. Catherine Wyrsch, for the faithful securing of the necessary specimens and the assistance in recording of results.

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SECTION VI—*Abdominal Surgery*

The Pathological Physiology of the Stomach Following Sub-Total Gastrectomy for Gastro-Duodenal Ulcer*

By

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WE have recently published a paper (8), in which we reviewed the pathological physiology of ulcerous stomachs in 123 cases. Now, we present here a complementary study of 70 of those cases after sub-total gastrectomy on the same basis, in order to judge the end-results, with reference to the treatment of gastro-duodenal ulcers. The technique followed in our cases, most of them operated on by Dr. J. Lastra, was that called the "Reichel-Hoffmeister-Finsterer" method.

The purposes of this study are the following:

(a). To determine, if sub-total gastrectomy creates a gastric pathological physiology, thereby producing pathological states other than those of ulcerous stomachs, affecting the digestive and nutritional functions of the patients.

(b). To ascertain if sub-total gastrectomy diminishes or eliminates the ulcer diathesis in every case.

EXAMINATION OF OUR GASTRECTOMIZED PATIENTS

We examined every patient in two different stages:

(1). At first, we exhibited in every one, the ordinary fractional Rehfuss test extending over three hours, using E. Boas' test-breakfast.

(2). Shortly after (on a different day) we performed either: (a) the histamine and neutral red tests, in those cases indicating an "achlorhydria" at the first examination, or (b) the vagal inhibition test, in the event of having obtained at the first examination, greater or smaller quantities of "residual free hydrochloric acid." We performed the histamine (one miligram hypodermic) and neutral red (4-5 c.c. of 1% solut.) tests following the ordinary standard techniques. The vagal function test was performed, comparing the acid figures before and after the injection of one millegram of atropin sulphate. These vagal inhibition tests have been done to show the *rôle* played by the vagus in the persistence of chlorydria after sub-total gastrectomy.

RESULTS

The functional disturbances found in our 70 gastrectomized cases, examined in a period of about 3 months after operation are:

Gastric motility: Hypermotility was found in a 54% (38 cases). It was very intense in the 27% (19 cases); hypomotility was found in 29% (20 cases) of which in 6% (4 cases) it was marked; normal motility was found in 17% (12 cases).

Bile reflux: We have found bile reflux in 47% (33 cases) in the fasting stomach and in 61% (43 cases) during the digestive cycle.

Acid secretion: We found hypersecretion in 8% (5 cases), hyposecretion 21% (15 cases), and normal secretion in 71% (50 cases). We found hyperchlorydria in 17% (13 cases) in the fasting stomach and in 23% (16 cases) during the digestive phase; hypochlorydria in 9% (6 cases) in the fasting stomach and 23% (16 cases) during the digestive phase; normal acidity was noted in 6% (4 cases) in the fasting stomach and in 3% (2 cases) in the digestive phase. Finally, we found "achlorydria" in 68% (47 cases) in the fasting stomach and 47% (33 cases) during the digestive phase maintained over three hours. The average secretion (amount of juice) in the 70 cases was 21.8 c.c., and the average of acidity was: free acid 7 vols. and total acid 27 vols. We also had 4% (3 cases of variable acidity.

Histamine and Neutral Red Tests: We had 21 cases with achlorydria in which we performed these tests. We performed the histamine test in 12 cases obtaining 83% of positive histamine responses (no reappearance of acid) and 17% with histamine negative test (reappearance of acid). We performed the neutral red test in 21 cases and we detected the elimination of the colored dye in every one of the cases, but one case was considered doubtful. The average elimination time was 32 minutes and 36 seconds.

Vagal function test: Only studied in cases with persistency of hydrochloric acid. It could be performed in 22 cases. Hyper-vagotonia (marked) was found in 18% (4 cases) and slight in 55% (12 cases); total 73%. Hypo-vagotonia in 27% (6 cases), but normal

*Preliminary report. Final report to be followed in two years or so. "Cuban contribution on gastrectomies" to reach a more favorable international approach. This paper will be published in detail, including tabulations in *Archivos de Medicina Interna*, of Cuba, Vol. 2, No. 1, Jan., 1936.

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vagus never was observed. In every case the free residual acid was modified more or less, proving evidently the main *rôle* of the vagus.

Mucous membrane condition: Alterations, including gastric cells, were present in 16% (11 cases) and without gastric cells 52% (37 cases). In 32% (22 cases), the gastric mucosa was normal. (As evidenced by microscopical sediment examinations).

All these results have been carefully noted in tabulations in our original manuscript but we are unable to include them here for lack of space. The complete records are displayed in the *Archivos de Medicina Interna.*, Vol. 2, No. 1, Jan., 1936, issued from Havana, Cuba.

COMMENT

The findings of our 70 cases of gastro-duodenal ulcer treated by sub-total gastrectomy according to the Reichel-Hoffmeister-Finsterer method, tends to show in 55% to 60% of the patients, the creation of a pathological physiology exhibiting the following principal features:

(a) Changes in motor function manifested by hypermotility and decrease of peristalis.

(b) An easily maintained bile regurgitation into the stomach.

(c) A more or less pronounced and permanent "achlorydria"; in most of the cases it does not respond to subcutanous histamine stimulation, but reacts with neutral red elimination, although the latter is somewhat delayed and of low intensity.

(d) A notable reduction of the diffuse inflammatory condition of the mucous membrane of the stomach (gastritis).

The significance of the pathological physiology of these sub-totally gastrectomized stomachs is definitely anti-ulcerous by virtue of creating a beneficial achlorydria with marked relief of the syndrome of vagal gastric irritability characterizing gastro-duodenal ulcers. The mechanism creating this curative syndrome after sub-total gastrectomy, consists in the elimination of hypervagotonia inherent to ulcers, and in the disappearance of the hormonal stimulus producing hydrochloric acid secretion, by the complete resection of the pyloric antrum. A correct technique is required and in some cases this syndrome after gastrectomy is modified by subsequent reappearance of acid secretion. In almost all these cases bearing the typical pathological physiology after sub-total gastrectomy, we have seen an absence of clinical symptomatology, particularly if additional post-operative medical treatment is followed. On the other hand, in those correctly gastrectomized cases with subsequent antiulcerous pathological physiology, a certain adaptation to the new anatomic and physiologic condition of gastric function is effected, compatible with a relatively normal digestive function. There ensues some widening of the gastric stump and in spite of the increased speed of emptying, the anastomotic loop which also widens, in its turn compensates for the relative gastric hypermotility. The alimentary contents are thus prepared properly for their satisfactory digestion. Thus it follows that there are no gross abnormalities in the stools, the indication of the deficiency of digestive function. (*Footnote*)

Footnote: This may occur more especially where Cuban patients maintain themselves on a diet which is high in carbohydrate and relatively low in animal protein and fat. Editor.

We wish to call attention to the fact that, in these correctly gastrectomized cases, the patients generally partake of a free national diet, as their social conditions will not allow them to undergo any additional dietary treatment. In the anastomized loop a true digestion, or chymification, replacing the normal one is carried out. This seems to meet the requirements of a standard digestive function. These comments refer to that 60% of cases with a normal course subtotal gastrectomy which has not met technical, operatory difficulties nor immediate or subsequent complications. We shall now discuss the cases in which the observations were otherwise.

In about one-third of the cases, the above mentioned desired end-results were not obtained. Another pathological physiology occurs closely resembling that of genuine gastro-duodenal ulcer. In these other cases, we observed a persistency of hypersecretion and hyperchlorydria accompanied by hypomotility and food retention. In other instances, there was a greater or lesser persistence of acidity varying in degree, and the clinical ulcerous sympthomatology reappeared sooner or later. In many of these cases, we proved that the operative technique had been faulty; however even after a quite correct operation, no anti-ulcerous pathological physiology was created and the condition remained like that in gastro-duodenal ulcer. These cases (25 to 33% of our series) justify the doubt of the surgeons who are opposed to sub-total gastrectomy, as to whether this procedure is capable of assuring an antiulcerous post-operative condition. The frequency of peptic ulcer formation, inflammatory constriction of the stoma, periviscerítis of the anastomotic opening, saccular dilatation, erosive residual hyperacid gastritis, etc., after gastrectomies performed by quite competent surgeons, make one doubt the advisability of considering sub-total gastrectomy a standard procedure for the treatment of gastro-duodenal ulcers. On the other hand, we are encouraged by the success obtained in most of our cases by our surgeons who have specialized in this type of sub-total gastrectomy. Referring to the truly inmediate surgical complications of gastrectomy, we must stress the point, that they ought not to be considered contra-indications as we have encountered few of these cases. The presence of paralytic ileus, hemorrhages and stump perforation in the postoperative records of our gastrectomized patients are very rare at present in our country.

In summarizing these considerations, we can affirm that because of the creation of an evidently antiulcerous pathological physiology, this type of sub-total gastrectomy appears to be the most effective operation, in view of its results, in the treatment of gastro-duodenal ulcers, when performed by specialized surgeons. Of course, it should be performed only on evidently established ulcers beyond the mucosa or accompanied by such complications as hemorrhage, perigastritis, etc. Gastrectomy should always be followed by adequate anti-ulcer medical treatment to facilitate the adaptation to the newly created anatomic physiologic conditions of the gastrectomized stomach and to avoid a deficiency of digestive and nutritional functions. Gastrectomy, performed by the average surgeon, who is not possessed of specialization in this type of operative technique, does not produce equally satisfactory results though it always proves to be superior to any

other conservative procedures in the surgical treatment of ulcers. After experience with all the conservative operations, particularly gastro-enterostomy, we found a persistency of the ulcerous pathological physiologic syndrome under the same or worse conditions.

CONCLUSIONS

1. To investigate the pathogenesis and therapy of gastro-duodenal ulcer, we studied by gastric intubation 70 cases in whom sub-total gastrectomy had been performed employing the technique of Reichel-Hoffmeister-Finsterer.

2. A complementary study of the gastrectomized patients with achlorhydria was accomplished by means of the neutral red and the histamine tests.

3. Particular attention was paid to the gastrectomized cases who exhibited persistent free hydrochloric acid in varying degrees, by means of the vagal inhibition test employing atropin.

4. We have summarized our findings and have presented as well, detailed comments on our findings according to the different functions (motility, bile reflex, secretion, chlorhydria, etc.), and have commented particularly on the data obtained through the neutral red, histamine, and vagal inhibition tests.

5. Alterations were found in 55-60% of the cases; these were characterized by hypermotility, pyloric insufficiency, changes in the gastric mucosa and achlorhydria. These achlorhydrias have, in 83% of the cases, positive histamine reactions (without appearance of free hydrochloric acid) and in 95% negative reactions to the neutral red elimination test thus proving them to be functional achlorhydria due to inhibition. This group of cases had been operated on mostly by our specialized surgeons.

6. The alterations found in 25-30% of the cases were characterized by persistency of free hydrochloric acid, and in many cases, by a marked hyperchlorhydria, hypomotility, with food retention and slight gastritis. The vagal inhibition test by the subcutaneous injection of one mgm. of atropin sulphate proved the active *rôle* of the vagus in the causative mechanism of residual chlorhydric acidity. Most of these cases had been operated on by very capable surgeons, though not specialized in gastrectomy.

7. Gastrectomy after the Reichel-Hoffmeister-Finsterer method acts as an anti-pathogenic operation for ulcer, by creating a genuine anti-ulcerous pathological physiology, particularly when performed with a correct technique and with a resultant good anastomotic opening. The resection of the pyloric antrum and vagal fibers ought to be as complete as possible in order to eliminate the hormonal and stimulating factors of the hydrochloric acid secretion.

8. A satisfactory adaptation to the newly created anatomy and physiology, with the assurance of a relatively normal digestive nutritional function is achieved.

9. It is advisable post-operatively to institute a complementary medical treatment directed against the ulcer diathesis and to facilitate the functional adaptation of the gastrectomized stomach.

10. Finally, sub-total gastrectomy appears to be the surgical intervention of choice; it is far superior to any of the various conservative procedures (gastro-enterostomy, etc.) for the surgical treatment of gastro-duodenal ulcers, though the best results are obtained when the operations are performed by surgeons who have specialized in this type of operation. The effects of sub-total gastrectomy even when performed with the best technique, are not completely adequate. There is always required a complementary medical treatment at the hands of one capable of appreciating the conditions present and capable of proper exhibition of that treatment.

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SECTION VII—*Surgery of the Lower Colon and Rectum*

Anal Cryptitis

By

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ANAL cryptitis is one of the commonest lesions causing, directly or indirectly, local anal symptoms. Directly, it is the source of prevalent subjective complaint; indirectly, because it is the essential nidus in the pathogenesis of the great majority of anal fistulas and their immediate sequelae, peri-anal abscesses. These latter conditions would, in other words, be comparatively rare but for the antecedent cryptitis. Furthermore, in contradistinction to other anal lesions, which may for the most part be recognized by palpation or inspection, the identification of crypts is not so

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simple, and requires more experienced search. If rectal carcinoma, for example, is so frequently overlooked because of failure to make even a cursory digital examination, how much more frequently must the more hidden secrets of anal pathology fail of revelation. For all of these reasons the topic would seem to justify more consideration than has in the past been accorded it.

We shall not interest ourselves at this time in the mentioned sequelae of cryptitis but only the uncomplicated lesion itself. And as further limitation I shall confine my notes largely to clinical considerations, and particularly as related to my own observations.

As an *anatomical and pathological introduction,* however, one should be familiar with the recent article of Tucker and Hellwig (3), which I particularly commend as a valuable and scholarly contribution toward a basic understanding of the condition. As an explanation of the *frequency* and *persistency* of cryptitis, these investigators have demonstrated the presence of preformed epithelial lined ducts, regarded as the remains of complex glandular organs as found in the lower orders of mammals, which open into the crypts of Morgagni and afford a ready path for infection. The infection was found to be primary in these ducts rather than in the crypts proper. The epithelial lining and poor drainage explain the failure to heal of themselves or with conservative measures, in conformity with generally recognized surgical principles. With one statement, however, I should like to take exception. Tucker and Hellwig state: "while the clinical importance of infected anal crypts is generally admitted—etc." I am constrained to say that their importance is not widely even *suspected,* that common knowledge regarding them is rather limited to those who are particularly interested in rectal work, and that patients may suffer for years because some little crypt is not found and eradicated. Anal cryptitis is the most frequently overlooked anal lesion.

The *local symptoms of anal cryptitis* vary within rather narrow limits. As is likewise the case with other anal conditions, complaint has usually extended over a long period of time when the physician is at last consulted, evidence of the universal antipathy for the hesitency of, rectal examinations. A crypt or several crypts, short or long, may be present without any symptoms whatsoever, and many such are found incidentally in the course of operations for other rectal conditions. The complaint for which relief is most often sought is what the patient relates to be "an irritation" and cannot further describe or classify; or it may be out and out pruritus. Either one or the other of these symptoms may be present exclusively, or they may merge one into the other at different times. As I write these lines, I am interrupted to see a boy of 19 years who has had almost constant itching for the past year. So aggravated has this been that whereas previously he had been a good student he did very poorly this year and quit school in disgust after extended treatment elsewhere. He has tried all the ointments suggested by numerous drug clerks and friends, in common with most patients who consult a proctologist. On examination, the only pathology found is a posterior crypt 1 cm. long which is determined to be, as later described, the source of his difficulty. Here, then, is a boy with a whole year of his life made useless, and possibly the whole trend of his existence influenced, by the failure previously to locate this crypt. The itching or irritation may be of a recurrent nature, appearing and disappearing at different intervals, which may vary from hours to days or weeks. I should like to emphasize this point and offer it as evidence in controversion of an elsewhere expressed opinion that pruritus is a neurosis which may be cured by the injection of a long lasting anesthetic, the latter supposedly curing the patient by diverting his mind for several days. That is, patients occasionally present themselves, who without any treatment at all have extended periods of relief, whose "vicious circles" are repeatedly broken by nature without cure. Likewise one should not be optimistic too early regarding any therapeutic procedure directed at pruritus, simple because a period of relief follows. The symptomatology of uncomplicated cryptitis does not extend to actual pain, that symptom indicating the presence of other pathology. I do not wish to imply that cryptitis is the sole cause of anal pruritus or irritation, but certainly it is a common cause.

I should like to say in passing that I do not see cases of pruritus, localized exclusively in the anal region, involving the general causes of pruritus reprinted every year in extended outline form. One can hardly pick up an article on pruritus ani without finding therein an elaborate classification of the causes: it is always the same, and is published and republished several times a year in the literature. General causes, remote, systemic, and reflex causes, are prominently displayed. No case reports are given, no claims for the relative frequency of such occurrences, no corroborative data whatsoever, but the list is always the same. A voice in the wilderness is that of Scarborough (1), who is so bold as to state that all cases are caused by pathological conditions in and around the anus. That is in keeping with my experience.

It is impossible to state with any degree of accuracy how frequently cryptitis is responsible for referred symptoms or for constituting a focus of infection. Wisely or unwisely, this is not so universally recognized a focus as the teeth and tonsils, etc., and so, many such cases may possibly be missed simply for lack of examination. Without rectal symptoms, these patients, would not of themselves, naturally, consult a proctologist. It would be the tendency of the internist, also, to overlook any such possible cases. (However I shall not say "these cases are probably more common than generally recognized." This so often used phrase is most superfluous. From the nature of things, and as long as the human mind is frail in comparison to its objective problems, the statement is true of any human ill. It should be deleted from medical literature). The recent case report of sciatica undoubtedly secondary to an anal focus of infection, reported by Smiley (2), is deserving of attention.

Usually offending crypts are quite easily located after one has acquired proficiency in anal examination in general and searching for crypts in particular, though sometimes they are located only by diligent and persistent search.

In the first place one is usually guided to the approximate location of the offending crypt by the location of the abnormal sensation or its most aggravated area, or, if extensive, the spot where it first appeared.

The responsible crypt is not found anteriorly when the symptom is posterior. Sometimes, on the other hand, it seems difficult or impossible for the patient to very accurately localize the symptom by spoken description, but he may be able to spot it with reference to a probe or other instrument placed successively on different parts of the circumference.

Then too, one is often guided by the presence of involved papillae adjacent to the crypt, they being noticeably swollen and reddened. Most frequently the offending crypt is found between two such pathological papillae.

One may enter, not just what just seems to be, but what actually is, a shallow and unoffensive crypt, and be content with letting the examination rest there. Further examination reveals what might be called a "secondary crypt," in communication with the first by a narrow neck. This secondary crypt may be narrow throughout its whole extent, an ordinary blind sinus, or may widen out so that the probe point can be swept back and forth under the skin margin for as much as a centimeter, the structures together resembling an hour glass in arrangement. The rounded head of the probe may slip easily into the secondary pocket, or it may go in with almost a snap, and the patient says, "Oh, that's tender there!", as the probe enters and is swept around. Sometimes the area is so sensitive that these secondary sinuses or extensions can only be fully entered after the area is anesthetized. Crypts may easily be overlooked in the folds of the mucosa and amongst the papillae, and only be found sometimes after repeated examinations on different occasions. The secondary extensions, too, are easily missed, due possibly to simply luck—or lack of it—but it is theoretically possible, and very probable, that the openings heal over, just like the external openings of fistulas, to break open at intervals, when they are more easily located. Whether these secondary sinuses or pockets are enlargements of the normally found ductal structures to which Tucker and Hellwig called attention, or whether they were originally but a part of the crypt and since separated by a partial or complete infective contraction, or whether they represent burrowing infections from the crypts or ducts one cannot say. Possibly they occur from various combinations. Practically, it makes little difference.

The *mode of examination* and the matter of instruments is important. The patient should be on his side, with the buttocks close to the edge of the examining table, the hips and knees bent at right angles, and the feet well away from the edge of the table so that the examiner seated on a stool can rest one elbow comfortably and with plenty of room on the table. The latter should be capable of being raised or lowered so that the position of the anus can be adjusted to eye level. The use of illumination permitting close, protracted, and comfortable scrutiny, is also essential; this cannot be accomplished by the light from a window nor by a large bulky head lamp, both of which devices do not permit close visualization. A reflecting head mirror is possible, but best of all is a small powerful light which projects from between the eyes. The Hirschman speculum gives a more satisfactory exposure of the wall of the canal then does the slide type of speculum, the wall being put on a slant corresponding to the bevel of the former instrument rather than parallel to the line of vision as with the slide type. It is important to have several sizes, and to use the largest tolerated, thus obliterating the folds of the wall making it as smooth and even as possible. Too often the attempt is made to do proctology with a single speculum or a single type of instrument. One finds the different types are valuable for different kinds of work, and it took me a long time to discover that a speculum could be manipulated as a retractor, allowing the examined side to be put on a stretch or released, as desired, thus adding considerably to the scope and thoroughness of examination.

One cannot examine satisfactorily for crypts with the ordinary operating room type of probe. It is necessary to have a long probe with a substantial handle, so that the instrument can be under adequate control with unobstructed vision. For examining (in contradistinction to operating) purposes, it is desirable to have the hook on the end rather short, about $\frac{3}{8}$ of an inch in length, and bent to a V shape rather than a U shape, and quite a wide V, the angle being slightly wider than that which the bevel of the speculum makes with the long axis of the speculum. Then about two inches toward the handle from the hook (about the length of the speculum) the shaft may be bent very *gently in the opposite direction*, a very slight angle, which helps to keep the handle out of the line of vision, and which is adjusted at the time of examination and may require changing from time to time even in the same case. These directions result in the ability to explore the side wall with *outward* pressure, rather than with a downward pull which is not in the direction of the long axis of the crypt and which results in hooking a small portion of the crypt—and so small a portion as to give the impression of a shallow and hence unoffending crypt—rather than demonstrating the crypt, with possibly a secondary pocket as described, in its demoniacal entirety. It is desirable to have at hand a number of probes of both fine and medium calibre with hooks of varying lengths from $\frac{1}{4}$ to $\frac{5}{8}$ of an inch long, and bent at different angles. For it is often inconvenient on spotting a suspicious area while slowly drawing the speculum out to have to stop and bend a probe several times until it fits the occasion. Having the various ones available in order obviates reintroducing the speculum over and over. Deliberation, care, and repeated examination are desirable, and often necessary.

Adequate treatment necessitates radical dissection of the crypt, preferably under local anesthesia. Linear incision by cryptotome or other instrument is useless, as recurrence will be inevitable. To perform the dissection expeditiously and with the least discomfort to the patient requires thought and practice.

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Annual Abstracts of Proctologic Literature

(May, 1934-May, 1935) By CLEMENT L. MARTIN, M.D., Chicago, Illinois

The complete bibliography from which these Abstracts were made will be published in full in the Transactions of the American Proctologic Society, 1935.

CHRONIC ULCERATIVE COLITIS

A very worthy contribution to this contentious subject is contained in the *Sibrand Lups'* thesis for his doctor's degree in medicine at Gronigen. It has been translated into English by Dr. A. J. Baker and appears in the *American Journal of Digestive Diseases and Nutrition.* Since 1922 when *Bargen's* work stimulated discussion of the disease and consequently more papers on it appeared, I have seen no more thorough and constructive a report of an investigation of the subject. His findings on animal innoculations, carefully controlled, support *Bargen's* conclusions as to the cause of the disease. He thinks one reason why some investigators failed to confirm the latter's results is that the virulence of the organism may diminish quite rapidly. Rapid isolation and culture are necessary as Bargen has indicated.

Another factor may be the marked variability of virulence of the organism itself. The diplostreptococci Lups used were from a very acute case.

Mogena studied eleven cases with severe ulcerative colitis, in eight of these Bargen's diplostreptococcus was the only organism found.

Shwartzman does not believe that the cause of the disease is established yet. Whatever the cause is, the mucosa may become vulnerable to its flora especially *B. coli.* He has prepared an anti-toxic anti-*coli* horse serum of high neutralizing titre as determined by means of local skin reactivity to *B. coli.* Of 21 cases treated with the serum he reports good results in 18 of 21 cases, failure in 3.

Felsen believes the cause of the disease is still unknown and states "it appears that some cases are the end result of a bacillary dysentery."

Bastedo suggests "At this stage (of our knowledge) might we not properly reclassify our cases into: ulcerative colitis with dysentery agglutinations and ulcerative colitis without dysentery agglutinations . . . . . ."

Thaysen writes on simple hemorrhagic proctitis and proctosigmoiditis divorcing it from chronic ulcerative colitis. Admitting there are cases which are mild, do not progress and are cured, this classification appears to me a step backward.

CYSTS

Enterogenous. *McLanahan & Stone* report two cases of enterogenous cysts associated with the rectum. The case histories are given; one patient was a woman of 48 years, the other a one-month-old boy. The majority of previously reported cases were of cysts in the ileocecal region.

In their own cases the cyst lining was definitely enteric. In their discussion the work of Evans, who emphasized the great preponderance of intestinal diverticula in early life, and Lewis and Thyng, who 25 years ago demonstrated the epithelial origin of these diverticula in the pig, rabbit and human embryos, is cited. The origin of enterogenous cysts is thought to be in these small diverticula and so it becomes easy to understand that such cysts and diverticula may in reality be different phases of the same process; thus it is not difficult to explain on the above basis the location of a cyst in the intestinal wall, be it submucosal, intermuscular or subserous. In addition, the tumor may lie at any point in the gut periphery, ante-mesenteric, mesenteric, or at an intermediate site. Many lie between the folds of the mesentery.

In a case report by *Hughes-Jones* of enterogenous cyst, the etiology is discussed from the standpoint of the origin of the diverticulum and from the basis of sequestration. *Pattison* writes of 6 cases of malignant lymphoma. The localized type is of special interest to the surgeon.

Cysts, Pilonidal. Twenty-one cases of pilonidal cyst were treated by *Ferguson.* After excision he used primary suture and had but one failure.

Oldham states he has had 100% cure in 19 cases of coccygeal sinus since 1933 by primary union following excision and suture with non-absorbable sutures.

Cattell excises the sinus after marking out a triangular flap. Excision is carried out, the flap mobilized and the wound sutured, closing the flap horizontally and longitudinally. My own experience with primary suture has convinced me that it has definite limitations. When once the incision becomes infected, as it very commonly does because of its site, the suture material acts as a foreign body to retain infection. Recurrence is perhaps more probable after primary union. As in any open granulating wound, a suspicious area may be curetted or excised; recurrences have been prevented in some of my own cases by careful post-operative observation. (See Transactions, 1934, Pilonidal Cyst, Rogers).

In a preliminary report of 6 cases examined by the Philadelphia post-graduate group in which pilonidal sinus or sinuses were injected with 5% methylene blue and X-rayed after Weeder's procedure, none of them showed communication with either sacrum or coccyx.

Cysts, Hydatid. Lockhart-Mummery reports a hydatid cyst of the rectum.

X-RAY

The present study, by Kantor and Schlechter, was undertaken: (1) to determine the range of mobility of the cecocolon; (2) to establish criteria for excessive fixation and excessive mobility and to report their incidence; and (3) to determine the clinical significance, if any, of these departures from the normal. The material used was an unselected series of 383 cases (190 males, 193 females). The normal vertical range of mobility of the hepatic flexure is over 1 inch to under 3 inches. Normal variation in the range of the cecum is from over 1 inch to 2½ inches. Hypermobility of the hepatic flexure may be said to exist when the vertical range is 3 inches or more, and hyperfixation when the vertical range is 1 inch or less. Hypermobility of the cecum may be said to exist when the vertical range is 2½ inches or more, and hyperfixation when the vertical range is 1 inch or less.

Excessive mobility in general occurs in 10% of cases and is associated with the asthenic habitus and with a high cecum. Excessive fixation of the hepatic flexure occurs in 28% of cases; of the cecum in 43% of cases; and of the cecocolon in 20% of cases. In general, excessive fixation is associated with low ceca or with duodenal bands. Clinically hypermotility of the hepatic flexure alone is associated with RLQ pain and tenderness and with a tendency to colonic stasis. Hypermobility of the cecum alone is associated with increased colonic irritability. Hypermobility of the cecocolon is a prerequisite for volvulus and intussusception. Clinically, hyperfixation of the hepatic flexure alone or of the cecocolon is associated with increased colonic irritability. Hyperfixation of the cecum alone is

apparently asymptomatic. The authors submit several drawings and six tables.

Kaplan outlines the types of cancer cases according to treatment facilities required, whether ambulatory, home, or hospital.

Bowing and Fricke give statistics on 500 cases of rectal carcinoma under radiation treatment. Radiation does not replace surgery but it has a distinct place in therapy of carcinoma of the anus, rectum and recto-sigmoid. Especially should the higher grade tumors be irradiated.

Weber reviews the development of gastro-intestinal Roentgen examination and stresses the importance of contrast enemas and insufflation of air following expulsion of contrast enemas in diagnosing colon conditions. Diagnostic efficiency is dependent on the examiner's familiarity with gross pathologic features of lesions as well as methods of examination.

Berg describes a method for examining the digestive mucosa by means of a thick watery suspension of opaque substance as a coating rather than a filling material. The stomach and intestine must be carefully emptied previous to examination.

DIVERTICULITIS

Various theories continue to be considered in an effort to determine the exact mode of formation of colonic diverticula. *d'Abreu* believes spasm and hyperactivity of the circular muscle of the bowel to be factors of great importance and he suggests that excessive parasympathetic action is a cause of these particularly inasmuch as relief is obtained by belladonna and hyoscyamus.

Edwards reserves surgery in diverticulitis of the colon for severe recurrent cases in which complications appear to be imminent. A right side colostomy should precede resection and should be done between attacks.

Weible suggests allowing diverticulitis of the sigmoid to go to abscess formation, then drainage being made through the anterior rectal wall by a tube extending through the anus.

Weber stresses the importance of contrast enemas after the method of Fisher and the insufflation of air following expulsion. Diagnostic efficiency is dependant upon the examiner's familiarity with the gross pathologic features of lesions as well as methods of examination.

Stewart and Illick in an article on the roentgenographic differentiation between diverticulitis and cancer of the sigmoid bring out several points of interest in a well illustrated article. They used but a pint of barium at first, examined the rectum and sigmoid thoroughly, thus avoiding confusion by other loops. The colon is then filled, and the entire procedure repeated after the patient has partially emptied the colon and again after complete defecation, often 24 hours after passing, as diverticula may be seen at this time which were not previously visible.

Lynch records a case of diverticulitis of the colon with abscess formation caused by an enema-tip injury.

FECAL IMPACTION

Stewart and Illick cite a case of obstruction from four large fecaliths and show in their article an excellent reproduction of the roentgenogram.

FISSURE, PAPILLITIS AND PECTENOSIS

The Philadelphia post-graduate group treated 4 cases of fissure by injection of Gabriel's A.B.A. solution; it proved painful and unsatisfactory in these few cases. One c.c. quinine and urea hydrochloride injections fared little better in three other cases. Using smaller amounts others have found them quite satisfactory in subacute small fissures. "Three fissures located in the posterior site were excised, after which the technic as outlined by Buie, namely, suturing the anal margin to the external sphincter muscle with catgut, was utilized. All three cases were followed by infection, and in one the sutures sloughed off."

Morgan reports 83 cases, which he operated, whose lesions could be explained by the presence of pectenosis and a pecten band. He concludes that pectenotomy is the method of choice and advises against the practice of divulsion in dealing with this condition.

SECTION VIII—*Editorial*

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastroenterological Association is in no way responsible for editorial expressions.

PHOTOGRAPHIC AIDS IN CONSERVING SPACE IN SCIENTIFIC PERIODICALS

IT has occurred to me many times that one solution to the difficult problem of publishing long papers would be to photograph all the tables and perhaps most of the graphs and reproduce them on one or two pages. Then the occasional investigator who wants certain details or who wants to analyze the data from a new point of view can copy out what he needs with the help of a magnifying glass. In some cases the whole paper or much of it might well be photographed in the same way and only the summary be set up and printed.

Doubtless at first there would be some complaining but writers would eventually get used to the method, and would see its advantages. The other day I was talking to a physician who had had an article published in the American Journal of Digestive Diseases and Nutrition. He was most appreciative of two things. One, that his article had been sent to the printer as soon as it was received, and the other that he hadn't received any annoying letter asking him to shorten the text and to cut down on the number of illustrations. It occurred to me that in many cases a writer would be so pleased with prompt publication of his whole paper that he wouldn't gnash his teeth because his tables were reproduced in miniature.

Unfortunately, it is a rare author who realizes that few readers ever read more than the summary at the end and that even fewer examine tables or complicated illustrations. Unfortunately, also, few authors realize how costly is the setting up of tabular material.

One great advantage of shortening articles would be the possibility of publishing more papers in each issue, which would make the JOURNAL more interesting and more valuable.

I think it probable that soon many physicians will become used to seeing technical material published in miniature. Already Science Service in Washington has arranged to supply books and copies of articles at an expense of a cent a page. Each page is photo-

graphed on motion picture film, and the microscopic text is read with the help of lenses which already are available for prices as low as $1.00. Larger and more comfortable reading devices will soon be available in all libraries.*

Once a physician becomes accustomed to reading reprints about an inch square, he will think nothing of seeing parts of the original publication put out in much of the same way. These innovations are upon us, so we might as well start getting used to them. Naturally, because of difficulties in printing and imperfections in the surface of magazine paper, the degree of reduction of the illustrations in a journal can hardly be as great as it is when film is used.

Walter C. Alvarez, Rochester, Minn.

*Note: Enlargements from films are available at five cents per page. These enlargements are approximately two-thirds of the size of commonly used manuscript paper. An author may have photographed on moving-picture films his whole manuscript and print but an abstract in a periodical. When correspondents request reprints, the author refers them to the holder of the films who then make enlargements from the films at the above mentioned nominal charge. Thus a periodical conserves space by printing only complete abstracts and authors are freed from the expense of buying reprints for gratis distribution. *Editor.*

SIGNIFICANCE OF VITAMIN A DEFICIENCY

CLINICAL and experimental observations within recent years have furnished conclusive evidence that vitamin A must be considered one of the most essential factors in nutrition. Vitamin A deficiency has been recognized in the past only when it reached an advanced stage, producing extreme malnutrition, with or without xeropthalmia. More recently interest has been aroused in the milder degrees of deficiency, the "twilight zone" of vitamin lack, with borderline states as described by Salter (1). Evidence is rapidly accumulating which suggests that permanent and irreparable damage to important organs may be produced by a prolonged or slight degree of deficiency in one or more of the important vitamins.

It has been demonstrated that the retina and cornea are especially rich in vitamin A and that their health and function are governed largely by the presence of this vitamin. Deficiency in vitamin A apparently effects the epithelial tissues in a specific manner. Eusterman and Wilbur (2) note the following in this regard: "The pathological investigations of Wolbach and Howe, subsequently confirmed by various other investigators, show that there is a substitution of stratified epithelium for normal epithelium in various parts of the respiratory, alimentary and genito-urinary tracts, in the eyes and in the para-ocular glands, or, in brief, metaplasia of the greater part of the ectodermal leaf of the body. Such changes may be followed by infection in the various organs or tissues. Thus, the maintenance of intact, healthy epithelial membranes, which constitutes the first line of defense against bacterial invasion is a prophylactic function of this vitamin of the first importance."

In view of the importance of what may be termed "chronic states of vitamin A lack," it appears essential that the early signs and symptoms characteristic of the condition should be determined, and a simple method for its detection provided. It may be added that once the diagnosis is established, the use of carotene in oil (a vitamin A concentrate) furnishes an efficient and dependable means of therapy.

A few years ago the appearance of an article by Jeans and Zentmire (3) directed my attention to the use of the visual photometer as a method for the determination of the amount of vitamin A in the human. The *rationale* of this method and its application in an extensive study of the state of vitamin A balance in over 275 individuals has been described by us in an earlier communication (4). In a more recent report (5) we presented a similar study of 300 individuals made during the past year, and correlated our observations on the vitamin A balance in various pathologic states with a review of the relavent literature.

Our experience with the visual photometer suggests that this instrument furnishes a simple but accurate method for the detection of vitamin A deficiency and an easy method whereby the clinician can check the response to treatment of the condition. The hundreds of tests made under our supervision showed decided uniformity in spite of the fact that they were made with the assistance of a number of different technicians.

In a large number of subjects who were considered deficient at the initial photometric test, increased vitamin A storage indicated later at a second test following carotene therapy was always coincident with the clinical improvement. Subjects in whom the photometer indicated no improvement also failed to show clinical benefit.

One of the most interesting results of our study was the high incidence (83%) of vitamin A deficiency indicated in a group of over a hundred supposedly normal individuals, or subjects whose only complaint was lassitude, nervousness, or a general lack of a sense of well-being.

This indicates that the diet of the average individual may not be complete and suggests the importance of the addition to the diet of a vitamin A concentrate to assure an ample supply.

It seems that a more accurate and extensive study should be made of the sources vitamin A in the commonly used foods, with especial reference to the marketing of fresh fruits and vegetables, together with a more careful checking and protection of the vitamin content of canned fruits, juices and vegetables.

Another factor which may in part account for the rather widespread deficiency in both vitamins A and D is a deficiency in fats in the average diet. These vitamins are fat-soluble and are best assimilated in the presence of fats.

The supplementary use of a concentrate is especially indicated when the diet is deliberately limited for therapeutic reasons or to cause reduction in weight. It is also indicated during the following infectious processes.

When studied with the visual photometer we found that all patients who had suffered recent attacks of pneumonia, bronchitis or other acute infections were deficient in vitamin A. The majority of these showed marked improvement with large doses of carotene in oil.* The past history of many of these patients indicated that their diets had been deficient in vitamin A.

Clinically one or more of the following symptoms

*Furnished through the courtesy of the S. M. A. Corp., Cleveland, Ohio.

was noted in individuals shown by tests with the visual photometer to be deficient in vitamin A: (1). General lack of vigor. (2). Fatigue out of proportion to the difficulty of the task or the age of the individual. (3). Lack luster of the cornea. (4). Nervous irritability and loss of sleep. (5). Dryness of the hair and roughening of the skin. (6). Ptosis of the eyelids. (7). Visual difficulties similar to those which are characteristic of night blindness.

Ira O. Park, Muskogee, Oklahoma.

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3. Jeans, P. C., and Zentmire, Zelma: *J. A. M. A.*, 102:892, 1933.
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ALLERGY AND THERAPEUTICS

IN the course of medical practice, clinical evidences of allergy frequently crop up. So bizarre and so unexpected may be allergic manifestations, that it behooves the physician to think of them when presented with anomalies which do not conform to accepted symptom-complexes depending on what we are pleased to call "organic" lesions.

Foods, feathers, fabrics, furs, pollens, perfumes, danders, creams, lotions, dyes, shoe polishes—the list is legion—any or all, to "susceptible" persons, may account for so wide a range of transient, or even permanent, functional, pseudo-organic or, eventually organic, upsets, that practitioners must, indeed, be possessed of super-wisdom or blessed with uncanny luck, if they escape confusing allergic states with essential disease.

It is of more than passing interest that not uncommonly by the agency of the very medicaments which physicians exhibit to treat disease, allergic states may be induced, much to the annoyance of patients and often to the puzzlement of their physicians. Cornstarch in powders, wool-fat in ointments, mint or other "flavors" in solutions or tablets, rhubarb in the old stand-by, *pulv. rhei comp.*, chocolate coating common to pills—scores of drug substances or the vehicles, coatings or fluids by which they are presented to patients in "sensitive" subjects, themselves may be responsible for a host of unique local or systemic deviations from the normal. And such departures not all are ephemeral or evanescent: serious organic damage to the liver, kidneys, lung, heart muscle or central nervous system may supervene upon massive dosage or what may be considered "safe," or even minute quantities, exhibited over prolonged periods.

Nowhere is this more strikingly shown than by the disastrous effects upon the liver following the administration of the salicylates or derivatives — notably cincophen—to susceptible individuals. Here and there one even reads reports of so widely used, and for years proved harmless, drug as the cathartic, phenolphthalein, being held responsible for allergic organ-damage to a fatal degree. True it is that, in certain instances where phenolphthalein has been set forth as being responsible for death in evidently susceptible persons, other drugs—as the salicylates—or bacteria or toxic food-derivatives may have brought about fatal issue, yet, as literature accumulates, it becomes evident that in certain infrequent individuals, phenolphthalein is capable of inducing the allergic state, quite as notably as are rhubarb, aloes and similar commonly prescribed cathartic medicines. Now that physicians' attention is directed to the matter, doubtless, as data are recorded, many usually employed medicinal agents will be found to be "toxic"—in the allergic meaning. Particularly will evidence become more extensive if individuals continue to "prescribe for themselves" and drug-shop clerks—not necessarily, pharmacists, for one observes few helpers of so high a grade, professionally or in general educational rating—continue to satisfy their demands. As conditions now exist, few, indeed, are the drugs which may not be purchased without physicians' prescriptions at average drug-shops, without or with the "sales' urge" of the person behind the counter.

Especially reprehensible is it that our central, state and local governmental incumbents find scant legal restraints, (or, if there are such, they ignore them), to the indiscriminate sale of drugs to whomever wishes them. And, in these days of economic distress, self-prescribing has become a widely spread custom: from relatives, friends, the corner druggist, periodicals, the ever blatant shrieks of the radio, nay from even *doctors, sick people learn the names of drugs or preparations* and then, wholly without knowledge as to whether such are suited to whatever ails them, buy from the nearest shop.

One cannot too strongly condemn the selling to any one with the price, of those drugs available in the form of medicated "candy" or chewing gum. Such are marketed in tempting form, the dose of drug per unit may not or may be stated in the package (if it is, the print is as "fine" as are the "trick," but all-important, paragraphs common to insurance policies); radio and newspapers proclaim unblushingly their miraculous virtues and, without let or hindrance, annually a large proportion of our population buys and consumes millions of units. Is it to be wondered that overdosing, ingestion of drugs over long periods or the taking of many and often incompatible "remedies" at times—as in the recently recorded instances of "phenolphthalein poisoning"—occasionally is followed by even fatal allergic response or in the absence of that, serious injury to esential organs? Such type of consequence to indiscriminate drug-taking, to be sure, calls for cautions in the exhibition of remedies to susceptible individuals, the recognition that certain persons *are* "sensitive" to even common drugs in therapeutic dose (rarely, however, have serious effects followed the taking of commonly accepted doses) but what is demanded is that politicians and congressional lobbies cease their pernicious activities and devote whatever brains and energy they may possess properly to safeguarding our citizens. Suitable laws which actually are enforced in an honest, scientific and non-political fashion, quickly could prevent reckless and careless dispensing. Until this much-desired, perhaps Utopian, situation is established, then drug poisoning—whether

"allergic" or from preposterous dosage—can be looked for with increasing frequency.

Of especial importance is it that physicians realize the possibilities of allergic manifestation occurring and when they do occur be prepared not only to treat the disability but to recognize that the origin of the illness may be in what previously have been considered common, harmless drugs or mixtures. They *are* such, unless they chance upon a "sensitive" subject or by constant use, they produce the "sensitive" state—a situation which rarely occurs when medicines are exhibited in accordance with physicians' orders. Meanwhile, hysteric or inexperienced writers should not fill the pages of medical journals with "clinical reports"—often questionable as to accuracy — condemning medicinal agents which years of use and after millions of doses have been shown to be harmless to the major portion of the population.

Frank Smithies.

SECTION IX—*Book Reviews*

(This section is open to contributions from any medical reader, whether or not a member of the Editorial Council).

The Patient and the Weather. By William F. Petersen, Vol. I, published, 1935, by Edwards Bros., Inc., Ann Arbor, Mich. Price $3.75.

IN his preface the author states with a good deal of justification that the young physician of today, with his training centered mainly about the infections, is not mentally equipped to evaluate, is seldom curious to study, and is rarely competent to treat properly a large group of chronic diseases. There is a great tendency to assume that all men and all guinea pigs are alike in their response to infection, and finally, too little thought is given to the fact that the environment may also influence the progress and the outcome of an infection.

This first volume is intended to serve as a rapid survey of the field of meteoric medicine. The author hopes to lead the physician back to Hippocrates and the Golden Age of Greece. As he points out in the second chapter, Hippocrates paid much attention to the state of the weather during the illness of a patient. Actually, Dr. Petersen might have added that 100 years ago William Beaumont still thought it advisable to make notes of the direction of the wind whenever he was studying the stomach of Alexis St. Martin.

The volume is largely a collection of maps of the United States showing with cross-hatchings of different densities the percentage incidence of various diseases and bodily defects in the various states and in the white and negro populations. Petersen believes that these maps show a greater incidence of most diseases along the track of the storms which, originating in the region about Japan, usually follow the coast of Asia and Alaska to enter the United States around Seattle. From thence most of them sweep through the northernmost two tiers of states, leaving through Maine and Newfoundland to go across the Atlantic and through Norway, Sweden and Finland to die out in northern Russia.

Naturally, the greatest variation in the weather in this country is to be found along this track, and as a corollary of this, here we find the greatest meteorologic demand for adjustment on the part of living beings. Dr. Petersen feels, therefore, that here one should expect to find the greatest abundance of human wreckage. He believes also that this greater stress on human protoplasm in the northernmost states accounts for the fact that there the people average high in intelligence while in the less stimulating South, the incidence of feeble mindedness is large. Similarly, in some states the people are radical while in others they lean toward fundamentalism. Petersen thinks he can explain also why Vermont produces more genius but also more insanity, also why tabes and paresis are more common in certain states, and why the Negro who lives to a ripe old age in South Carolina, in the North becomes a problem for health officers.

There is no question but that the facts charted in these maps deserve much thought and study, and a man could probably spend a lifetime searching for the causes underlying the different incidence of diseases in the several states.

Although the reviewer is filled with admiration for Doctor Petersen's tremendous industry in collecting and presenting the data, and although there is much in the theory that is attractive and plausible, he cannot yet accept as even probable many of the deductions made. Actually the book would be more satisfying if Doctor Petersen had only presented his maps with the bare suggestion that possibly the storm track has something to do with some of the peculiar heavy incidences of disease in the northernmost states. An enormous amount of careful work would have to be done before any definite conclusions could be drawn, and Doctor Petersen would doubtless make more converts to his views if he were to lead his readers more gently and more surely along the ground, facing meticulously every objection and mentioning every other possible explanation for the observations made.

In all this work Dr. Petersen should have at his elbow a number of devil's advocates: one a man highly trained in the interpretation of vital statistics, another a teacher of logic, and another a careful student of trends of population in the United States. This man would know why California is full of invalids and old people, why Florida and Texas are no longer southern states, and from whence came most of the people seeking health or recreation, or oil. Dr. Petersen should have at his elbow someone to remind him constantly of how carelessly and hurriedly the draft examinations were made, and how incomplete and valueless are most of the mortality statistics based on reports by general practitioners, especially in the more backward communities. As a pathologist, Petersen must know what a tremendous difference there commonly is between the diseases that are found at a

necropsy and those which are listed on the history sheet filled in before the death of the patient.

Looking at the maps, one finds for example, that the incidence of goiter is high along the western two-thirds of the storm belt but it is very low at the eastern end. Is it not probable then, that the incidence of goiter has little to do with the weather and much more to do with the amount of iodine in the soil. Similarly, one can blame only indirectly on the storm track the tremendous incidence of tuberculosis in California, Arizona, North Carolina and New Mexico. One would be inclined to look for some decided reason for the high incidence of multiple sclerosis in drafted men from Minnesota, Michigan, Connecticut and Delaware. But does this high incidence appear also in the United States' mortality statistics, and has it been constant for any length of time? It would not seem to be due to the storm track because other states along this track are practically free from the disease.

No statistically minded person would ever feel like accepting inferences from Dr. Petersen's maps until corrections had been made for age of population and for the tendency of invalids and aged persons to crowd into certain states like California and Florida. Great care would have to be taken also to avoid drawing inferences from such facts as a high mortality from cancer or brain tumor or several of the rare diseases in Minnesota or Maryland where the presence of a large medical center attracts thousands of people close to death. It would seem that this influx of dying people must affect the mortality and morbidity statistics of some states.

Perhaps a safer and a simpler way of getting at some of these problems of meteorologic medicine would be to compare the incidence of disease in different universities within and without the storm track, as observed by able physicians in the student health services. If the reviewer remembers correctly, such a study, made years ago of the incidence of colds at the universities of Michigan and Stanford, showed no particular difference.

With all his objections, the reviewer does not wish to be understood at decrying this type of study. To him it is fascinating and well worth the labor of a life-time. He wishes Dr. Petersen well; he fears only that the doctor's tendency to blame everything including eclampsia on the weather will antagonize the very men who would gladly go along with him. It would seem a wiser course never to mention an effect of weather until the proof of the association is convincing, and all other possible explanations have been disposed of.

Walter C. Alvarez, Rochester, Minn.

SECTION XI—*Societies, Programs and Proceedings*

Thirty-Seventh Annual Meeting American Proctologic Society

Kansas City, Monday and Tuesday, May 11 and 12, 1936

HEADQUARTERS: The Kansas Citian

ARRANGEMENTS:
Dr. Fred B. Campbell, Dr. Daniel Morton,
Dr. George H. Thiele.

THE AMERICAN PROCTOLOGIC SOCIETY, organized in 1899 for the purpose of "investigating and disseminating knowledge relating to the rectum, anus and colon," is a society with a definitely limited membership, divided into Fellows, Associates, Honorary Fellows and Honorary Associates.

Regular and orthodox practitioners, members of the American Medical Association, and not affiliated with medical groups admitting those not members of the A. M. A., are hereby cordially invited to attend the 37th Annual Meeting in Kansas City, Monday and Tuesday, May 11 and 12—the week of the A. M. A. meeting.

Physicians fulfilling the above requirements who are especially interested in Proctology are eligible to submit applications for Associate Membership after attending at least one meeting of the Society and one meeting of the American Medical Association Section.

For additional information, address the Secretary.

CURTICE ROSSER, M.D., F.A.C.S.,
710 Medical Arts Bldg., Dallas, Texas.

TENTATIVE SUMMARY OF EVENTS

SUNDAY, MAY 10

12 Noon—Registration. Kansas Citian.
2 P. M.—Ride over Kansas City and environs.

MONDAY, MAY 11

8:00 A. M.—Registration. Kansas Citian
9:00 A. M.—First Scientific Session. Kansas Citian.
12:00 Noon—Luncheon. Kansas Citian.
1:30 P. M.—Second Scientific Session. Kansas Citian.

8:00 P. M.—Executive Session. Kansas Citian. Fellows only.

TUESDAY, MAY 12

8:30 A. M.—Third Scientific Session (Symposiums). Kansas Citian.

12:30 P. M.—Luncheon. Kansas Citian.

2:00 P. M.—Operative and Dry Clinics. The Kansas City General Hospital. Dr. Campbell and Associates.

8:00 P. M.—Annual Proctologic Society Dinner. K. C. Athletic Club. (Registered guests invited).

WEDNESDAY, THURSDAY, FRIDAY

Section on Gastro-enterology and Proctology, American Medical Association.

THE SCIENTIFIC PROGRAM

Presidential Address:
Dr. Frank G. Runyeon, Reading, Pa.

Report of Committee of Arrangements:
Dr. Frederick B. Campbell, Kansas City.

Memorial to Dr. Linthicum:
Dr. A. B. Graham, Indianapolis, Ind.

Review of the Literature of 1935:
Dr. Chas. E. Pope, Evanston, Ill.

Report of Committee on Physiotherapy:
Dr. E. H. Terrell, Richmond, Va.

CASE REPORTS

(Speakers are allotted five minutes, and there is no discussion).

Fistula in Ano with extension to lower limb:
Dr. Hugh Beaton, Fort Worth, Texas.

Cases of Imperforate Anus:
Dr. W. W. Green, Toledo, Ohio.

Fistula, Pilonidal Sinus, Cowperitis in one individual:
Dr. A. G. Carmel, Cincinnati, Ohio.

Cancer in Vestigial Neurenteric Canal:
Dr. Harry C. Guess, Buffalo, N. Y.

Factitial Proctitis:
Dr. Nils O. Byland, Battle Creek, Mich.

FORMAL PAPERS (15 Minutes)

The Variety and Distribution of Gross Lesions in Lymphopathia Venerea:
Dr. Collier F. Martin, Philadelphia, Pa.

Fistula in Ano (Motion picture presentation):
Dr. Dudley A. Smith, San Francisco, Calif.

Anterior Lymphatic Abscess:
Dr. Louis A. Buie, Rochester, Minn.

Drainage in Certain Anorectal Operations:
Dr. Louis J. Hirschman, Detroit, Mich.

Pruritis Ani (Report of cases treated by injection of distilled water):
Dr. Harry E. Bacon, Philadelphia, Pa.

Injection Treatment of Prolapse of the Rectum:
Dr. F. B. Bowman, Hamilton, Ontario, Canada.

Association of the Proctologic and Urinary Tracts:
Dr. Frank H. Murray, Chester, Pa.

THE SYMPOSIUMS

The Session on Tuesday morning will be set aside for three symposiums on phases of proctology of definite current importance:

DIVERTICULOSIS AND DIVERTICULITIS

Pathological Considerations:
Dr. Emsley T. Johnson, Pathologist to St. Joseph Hospital, Kansas City. (By invitation).

Clinical and Therapeutic Status of Colonic Diverticulosis:
Dr. Henry LeRoy Bockus, Professor of Gastro-Enterology, Univ. of Penn., Graduate School of Medicine, Philadelphia. (By invitation).

Surgical Management of Colonic Diverticulitis:
Dr. Thomas E. Jones, Cleveland.

Discussion opened by:
Dr. Fred Rankin, Lexington, Ky.

CAUSES OF HIGH RECTAL AND LOW BACK PAIN

Tonic Spasm of the Levator Ani, Coccygeus and Piriformis Muscles; Relationship to Coccydynia and Sciatica:
Dr. George H. Thiele, Kansas City.

Rectal Pain Associated with Sacro Illiac Strain:
Dr. Malcolm R. Hill, Los Angeles, Calif.

Discussion opened by:
Dr. Frank Dickson, Kansas City. (By invitation).

PILO-NIDAL SINUS

Etiology, Pathology, Diagnosis:
Dr. William Strobel, Duluth, Wis.

Surgical Management:
Dr. Martin S. Kleckner, Allentown, Pa.

Discussion opened by:
Dr. Walter A. Fansler, Minneapolis.

THE AMERICAN MEDICAL ASSOCIATION

In addition to the informative papers which will be heard at the annual meeting of the Society, the tentative program of the Section covering the specialty during the A. M. A. meeting immediately following indicates that the following subjects of special interest will be presented before that body:

Multiple Polyposis (McKenney)
Disseminated Polyposis (Mayo and Wakefield)
Etiology of Pruritis Ani (Tucker and Hellwig)
Surgical Treatment of Pruritis Ani (Pruitt)
Routine Colon Examination (Hirschman)
Carcinoma of the Rectum (Brindley)
Recurring Carcinoma of the Colon (Thompson)

LADIES ENTERTAINMENT

The wives of all members and guests are assured that every effort will be made by Mrs. Campbell and her Committee to add to their pleasure during the meeting of the Society.

HEADQUARTERS

The Kansas Citian Hotel. The Registration table for both doctors and their ladies will be maintained at the Kansas Citian. The usual registration fee of $5.00 will be in effect and will be applied, as is customary, to all registrants, including members of families.

THE ANNUAL TRANSACTIONS FOR 1935

have been published in one volume, which may be procured from the Editor, Dr. Herbert I. Kallet, Macabees Bldg., Detroit, upon remittance of $5.00. This volume contains a full record of all the papers and discussion of the 1935 meeting in Atlantic City, is well illustrated and handsomely bound.

SECTION XII—"*The Clinic*"

Obstipation with Long Continued Vomiting: Effect on the Teeth*

By

J. ARNOLD BARGEN, M.D.**†

and

LOUIE T. AUSTIN, D.D.S.†

ROCHESTER, MINNESOTA

A WOMAN, aged twenty-six years, who was a school teacher and a native of Mississippi, came to this clinic on June, 22, 1935, because of life-long constipation which had been very obstinate. She never had had bowel movements without the help of cathartics or enemas. As she had become older, this condition had become worse. Twelve years ago, she had begun to vomit occasionally; this had become progressively worse so that during the last six years she had vomited after nearly every meal. The last few years, the vomiting had been somewhat projectile and had occurred almost as soon as food had reached the stomach. She had consulted many physicians, without any substantial relief. Early in 1935, the value for the serum calcium had been found to be decreased and parathyroid extract and calcium gluconate had been prescribed. About the same time, injections of surgical pituitrin had been begun; these, plus an enema, had

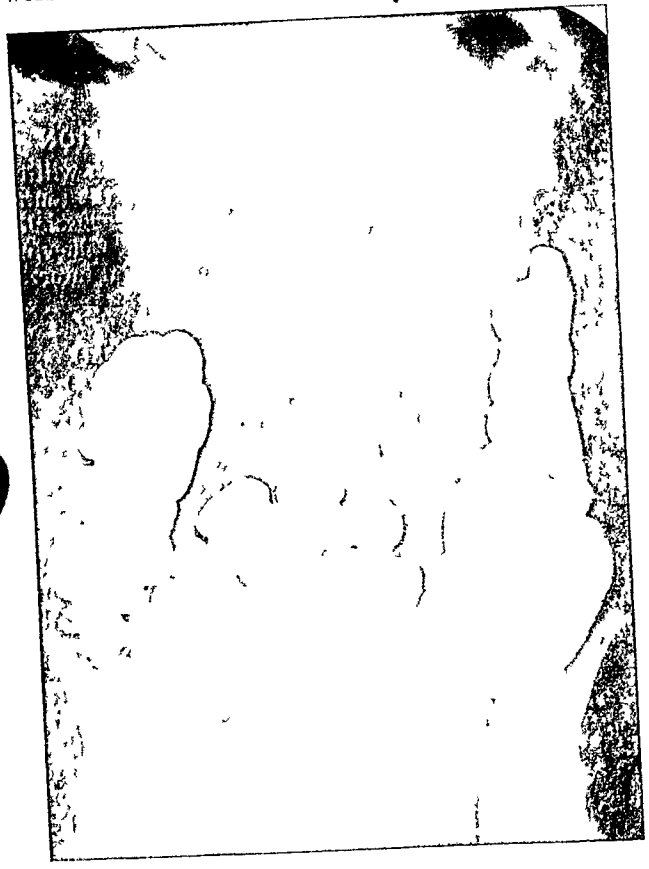


Fig 1. Elongated and dilated colon.



Fig. 2. Two views showing erosion of the anterior teeth as the result of long standing emesis.

**Division of Medicine, The Mayo Clinic
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Submitted November 26, 1935

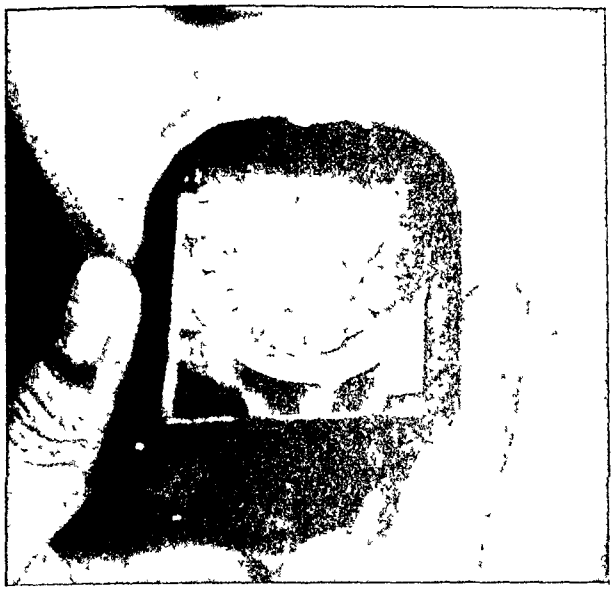


Fig. 3. Effect of long standing emesis on the teeth with fillings.

yielded bowel movements, and since the evacuations had been so much more satisfactory than they had been previously, she had continued this treatment for many months.

When she was examined at this clinic, her weight was 72 pounds (32.7 kg.) and her height was 5 feet, 4 inches (162.6 cm.). The values for the systolic and diastolic blood pressure were 92 and 58 mm. of mercury respectively. She was literally a "walking skeleton." The value for the hemoglobin was 9.7 gm. per 100 c.c. of blood. The erythrocytes numbered 3,460,000, and the leukocytes numbered 3,600 per cu. mm. of blood. A differential count of the leukocytes revealed the following values: 41.0 per cent for the lymphocytes, 4.0 per cent for the monocytes, 51.0 per cent for the polymorphonuclear neutrophils, 2.0 per cent for the eosinophils, and 1.0 per cent for the basophils. The values for the gastric acidity were 40 and 20, respectively, for the total and free hydrochloric acid with a 120 c.c. test meal, and according to the method of Topfer. Roentgenologic examination of the stomach, esophagus and duodenum did not reveal any abnormality. Roentgenologic studies of the colon showed it to be long and somewhat dilated (Fig. 1). There was no evidence of intrinsic disease. Numerous urinalyses disclosed that the urine was normal. A peculiar finding was the erosion of her anterior teeth (Fig. 2) and occlusion. One of us immediately suspected that these dental changes were the result of the continuous and repeated vomiting. It will be noted that her anterior teeth do not strike because of loss of substance, and that only her molar teeth are in occlusion. It was found that the lingual surfaces of all anterior teeth were affected, both upper and lower. The enamel had disappeared and the underlying dentine was exposed. The labial surfaces were not affected at all. The incisor teeth were shortened considerably and the incisal margins were very sharp. In the molar teeth the occlusal surfaces were chiefly involved. Fillings appeared as elevated islands of metal (Fig. 3).

The saliva had a pH of 8.0; her saliva probably had been normal at all times.

The patient became aware of the dental condition about three years ago, because of sensitivity to thermal changes and so forth, with gradual increase of discomfort. The teeth were very sensitive and protective measures were inadvisable until regurgitation was controlled. This condition is similar to erosion which results from the use of hydrochloric acid in the treatment of achlorhydria. In such cases the labial surfaces of the teeth are decalcified. It was learned that vomiting had occurred some little time after eating and that her food had been swallowed several times. Rumination is rather common among human beings, and probably not much damage is done to teeth except when it occurs at night and allows the gastric contents to remain in the mouth for a long time. The habit occasionally may be responsible for the condition spoken of as "soft teeth."

After a thorough discussion of the condition, a rigid anticonstipation diet was given. Three liters of liquid daily, and 15 drops of tincture of belladonna three times a day were given. She was also given 1/60 grain (0.0011 gm.) of physostigmine salicylate, twice a day, by mouth. The bowels began to move, the vomiting ceased, and during a period of weeks there was a gradual return of normal function. As this occurred, the administration of physostigmine salicylate was discontinued. When she was dismissed, she was advised to take a bulky type of diet and adequate amounts of liquids. During the six weeks in which this program was continued, she gained 10 pounds (4.5 kg.) and felt very well.

ABSTRACTS

CLINICAL MEDICINE

SNELL, ALBERT M.

The Effects of Chronic Disease of the Liver on the Composition and Physio-Chemical Properties of Blood; Changes in Serum Proteins; Reduction in the Oxygen Saturation of the Arterial Blood. Ann. Int. Med., IX, 690, Dec. 1935.

The author's thesis is that recognition of the unusual power of the liver to regenerate and of its very large functional capacity does not explain the freedom of symptoms in many cases in which extensive anatomical lesions exist. The studies in this paper were directed toward searching for some changes in the blood which might explain the ability of the liver to carry on when apparently showing an advanced disease in one group of cases, whereas, in another group much less anatomic changes obtain, yet all the signs and symptoms of advanced hepatic disease are found.

From these clinical observations he proceeded along two lines in search of the changes which appeared to lead to progressive disintegration of the hepatic structures, as well as, alterations in the physiological content. The studies were directed to changes in the blood in two directions, (a) the probable relation of the liver to the maintenance of serum protein; (b) the changes in the oxygen content of arterial blood, secondary to hepatic disease.

He found a fairly uniform disturbance of the normal albumin-globulin ratio, though the total proteins were not necessarily reduced; attention is invited to the rapidity with which the changes in total protein and albumin-globulin ratio occur, and he suggests that these changes possibly have some prognostic significance; that the degree of malnutrition in many cases was not conspicuous, thus making it difficult to explain the rapidity of variations on a nutritional basis; that feeding of protein had little effect on either the total serum protein or the albumin-globulin ratio. He agrees with other authors that the loss of protein through the ascitic or edema fluid does not seem to be a factor. He believes that clinical and experimental evidence seems to indicate a failure of production of protein or protein-building substances on the part of the liver with a disturbed equilibrium between the protein which is circulating and the protein which is stored. He concurs with the generally accepted belief that the reduced albumin content of blood serum of patients with hepatic disease is closely tied into the production of ascites and edema. He did not often find that the total serum proteins had been reduced to the "edema level" (4 to 5 gm. per 100 c.c.), but thinks that the disproportionate reduction in the serum albumin lowers the osmotic pressure of blood serum sufficiently to result in transudation, particularly when venous stasis occurs. He believes that such conditions as portal venous stasis and chronic peritoneal irritation play an important part in the production of ascites in hepatic disease and that the diminished serum albumin is a contributing factor only. He concludes this phase of his study with the following summary: "that one of the fairly constant effects of parenchymatous hepatic disease is reduction in the serum albumin and reversal of the albumin-globulin ratio; that these changes are most probably related to deficient production of protein by the liver, and that for this reason it may have some diagnostic and prognostic significance; and, finally, that the serum albumin is almost at or near a level which makes the production of ascites and edema relatively easy".

Turning to a discussion of the possibility of anoxemia as a factor in hepatic disease, after calling attention to the literature on the subject and describing his method and technical details, he quotes some cases upon which to predicate his theory and conclusions. The result can be no more briefly stated than to quote his own summary. "There are no constant demonstrable changes in the lung or circulation which explain the anoxemia curve in cases of advanced hepatic disease; minor degrees of edema of the alveolar walls cannot be excluded; mechanical factors such as ascites and abdominal distention are not necessary for its production; to date it has been impossible to demonstrate any variations in the physiological behaviour of hemoglobin sufficient to explain the difficulty with which the blood of these patients takes up oxygen. So far as the effects of anoxemia on the symptoms and course of the disease are concerned, it suffices to say that anoxemia, if of considerable degree and duration, can have only one effect, and that this would be an unfavorable one. It would also appear that the patient who has a chronic hepatic lesion is poorly equipped to adjust himself to even the less severe degrees of anoxemia because of the limitation in production of hemoglobin. Although the evidence is admittedly incomplete, there is much to suggest that anoxemia is at least one of the factors in which a vicious circle of progressive disintegration of the hepatic parenchyma is established."

The relation of the following problems to the anoxemia in hepatic disease is still under investigation. 1. Are there changes in the physical character of the blood which retard the rate of its oxygenation in the lung? 2. Are there hypothetical changes in the physiological behaviour of hemoglobin which can be shown only by a consideration of the time required for its complete oxygenation? 3. Is the behaviour of the pulmonary alveoli as a site for oxygenation altered in some manner, possibly by changes in the alveolar wall with resultant difficulty in diffusion of oxygen, the so-called Brauer's pneumonosis, or does the engorged or contracted liver with its mechanically altered blood flow decrease the rate of filling of the right auricle and indirectly reduce the rate of blood flow through the pulmonary capillaries, thus reducing the speed at which blood can be oxygenated?

Virgil E. Simpson, Louisville.

MAYER, O. B.

Enteric Cysts. Ann. of Int. Med., Vol. IX, p. 797, Dec. 1935.

The author reports a case of an enteric cyst in a boy twelve years of age with symptoms of only a few days duration and a diagnosis made only after microscopic study. The X-ray report suggested a pancreatic tumor, possibly of a cystic nature, and the preoperative clinical diagnosis was that of a probable pancreatic cyst. This diagnosis was based on the history of an abdominal injury, the location and apparently rapid development of the tumor, the X-ray findings and a Sugar Tolerance Test.

The case is interesting because of (1) its unusual location in the transverse meso colon; (2) large size, constituting about 1/25 of the entire body weight; (3) its attachment, which permitted the removal of the cyst intact without disturbing the adjacent intestines; (4) the satisfactory postoperative convalescence.

Accompanying the report is a short reference to the nature of these cysts, the theories as to their origin and reference to some reported cases in the literature illustrating their anatomical location. These cysts are structurally similar to the intestines. They contain a mucoid substance and are lined by epithelial cells with an underlying layer of lymphoid tissue and smooth muscle.

One theory as to their origin is that they spring from a bud or pouch along the intestinal tract and another is that they are related to the more common diverticula of childhood. The majority of the cases have occurred in childhood, though some have been reported in both extremes of life. The total number reported to date is 28, the first one being reported by Franckel in 1882. The most of the cases have been found in ileocecal areas, which may be due to the fact that there is here found a remnant of the vitelline duct or yolk sac. (It is well known that when the proximal end of this pouch remains patent, the result is a typical Mechael's diverticulum.) Partly because of their rarity these cysts are seldom diagnosed except at operations.

Virgil E. Simpson, Louisville.

SIMONDS, J. P. AND JERGESON, FLOYD H. *Late Changes in the Liver Induced by Mechanical Obstruction of the Hepatic Veins. Arch. of Path., 20:4, Oct. 1935, p. 571.*

The authors have attempted to approach the subject of experimental cirrhosis of the liver from the standpoint of mechanical obstruction of the hepatic veins. They report the structural changes found in the livers of dogs as seen from the 7th to the 60th postoperative day following the mechanical obstruction of these veins for periods of from 10 to 50 minutes. They found that the dog's liver can withstand complete or almost complete stagnation of its circulation for periods of from 30 to 50 minutes with relatively slight structural changes and functional disturbance. The reason for the lack of these changes is probably the fact that the liver normally uses relatively little oxygen as compared, for instance, with that of the kidney and the brain. The amount of oxygen used by the liver of the cat, as reported by Winterstein, is about 1.1 cc. of oxygen per 100 grams per minute; that of the kidney 2½ times and that of the brain 9 times greater. Other factors may enter into this protective mechanism. The outflow from the thoracic duct is increased 2½ times during obstruction of the hepatic veins. Certain of the normal functions of the liver, such as detoxication, deamination, formation of urea and glycogenic activity may be factors protecting the hepatic cells against the effects of anoxemia.

No structural changes comparable with a true cirrhosis were produced. Certain changes were observed, however. Swelling and granulation of hepatic cells, seen frequently in the early stages, were still present in one dog on the 52nd postoperative day. Swelling of the hepatic cells from either hydropic degeneration or intracellular edema with collapse of the sinusoids remained in the later stages. Fibrosis of the walls of the central veins was evident in the later stages also. This was the only increase in connective tissue found. None of these progressive or continued degenerative changes resembled true cirrhosis of the liver.

N. W. Jones, Portland, Oregon.

EXPERIMENTAL PHYSIOLOGY

ROUQUES, LUCIEN.

"Urticaria." (A special number entirely devoted to the question in the review, "Nutrition," Paris, Tome 5, No. 1, 1935).

Urticaria to heat or cold. Pathogenesis and treatment. In these cases we have to do with a general reactivation of the organism towards cold and heat and with the vaso-motor system, excited by the colloidoclasic crisis, accompanied by a phenomenon of shock without the intervention of an extrinsec antigen. This would be due to autoanaphylacy.

Urticaria to heat. The author doubts the existence of such an urticaria, and believes these conditions belong to digestive urticaria appearing after and due to the heat of the bed or the sun, and then produced by certain spectral rays, without shock, or *would be* due to perspiration, the eruption appearing after an abundant perspiration, whatever the cause may be. The acidity of sweat is held responsible, but the *rôle* of the heat is unquestionable. A case report is given of a patient showing spells of rash or eruptions with pruritis under the influence of three factors: physical effort, mental effort (discussion, quarrel) and heat in a certain point of the body. The spells were accompanied by itching with eruption, increase in the central temperature and blood eosinophilia at 10%; cold had no effect on this patient. This case showed a reflex action of the nervous system which caused a drop of the leucocytosis from 6000 to 3000. Hemoclasia is still to be proved in those instances and instead of a casal process, we might have to do with a co-ordinated process.

Urticaria to cold. This form is observed whether after an exposure of the subject to the cold outdoor temperature, or to a local refrigeration, after the immersion of the hands in water.

Humidity and wind would be necessary with cold to have a causal effect. Some individuals reveal urticaria following river baths, whereas surf bathings produce no effect, or, when passing from warm bath into a cold atmosphere. Urticaria is produced chiefly after a sudden cold, whatever the cause may be: air, water, ice, ethyl chlorhyde, carbonic snow or ether evaporation. In all these cases cold plays a primary rôle and pathogenesis remains the same. The eruption has been noticed as superimposed on the refrigerated zone without going beyond it. No generalized eruption is noticed.

Interpretation. This condition can be considered as a local vaso-motor reaction or as phenomenon of shock.

Local reaction. Its rôle would be, in these cases, unquestionable. Eruption starts in the refrigerated zone even in a generalized rash. The origin is sympathetic. Some authors adopt a mixed theory: humoral, nervous, or perhaps cellular. One must admit with Widal, Abrami and Brissaud, that autocolloidoclasia by cold is undoubtful. According to humoral reactions, these patients can be classified in three groups.

First group: no hemoclasia. In those cases the humoral reaction is absent or not registered.

Second group: atypical reaction. The immersion of a hand or forearm in ice water is accompanied in certain patients with leucopenia, inversion of the white cell formula and hypertension. In others, hypertension is replaced by hypotension with leucopenia, without inversion, etc. An alternation between vaso-dilation and vaso-constriction is noticed. A series of observations is quoted by the author showing leucopenia on the cold side and increased leucocytes in the other members, the leucopenia passing from 12,000 to 15,800 in the left arm, after taking the right arm out of the ice, the formula coming back to normal after 12 minutes. These white cells variations are observed also in healthy individuals. Consequently, leucopenia has no signification to show evidence of a "shock" process incited by the digestive absorption of an antigen, not more than urticaria to cold incited by cold. This leucopenia by cold is merely *mechanical* and, as the author says, "the anaphylactic shock is essentially indicated by violent reactions of splanchnic origin proving a deep perturbation of the entire organo-vegetative system."

The opposition between the blood formula of the periphareal veins (leucopenia) and the central ones (absence of leucopenia) during the hemoclastic shock by cold on one hand, and hyperleucocytosis and transsitory leucocytosis on the other hand in the heart and blood vessels, is too complex a phenomenon to be explained by a simple peripheric vaso-constriction.

Third group: hemoclastic "crisis." It is revealed by leucopenia, hypotension and appearing in individuals presenting urticaria *"a frigore"* and the relations between shock and eruption are questioned by the author. In some individuals, the eruption precedes; in others, follows, crisis. From a biological standpoint, it is affirmed by the authors that the hemoclastic "crisis" must precede the clinical accidents, although cases have been observed where local urticaria appeared immediately after immersion of the member into ice, whereas, in others, it is more tardive before generalizing. In the former, it is a merely local vaso-motor reaction

caused by cold, and in the latter instance, it is the consequence of a general shock. This phenomenon is chiefly observed in patients with hemoglobinuria. A case is quoted of a man who, ducked in a cold bath, suddenly showed various troubles with collapsus and repeated lypothemias, followed by an eruption 15 minutes after the bath. Obviously, this case of tardive urticaria is due to collapsus. Frequently also, hemoglobinuria (paroxystic) with hemolysis is observed.

Urticaria to cold. Whatever the pathogenesis may be, shock to cold exists. According to certain authors (Widal) "cold suddenly dissociates certain plasmatic colloids already combined, and this sudden dislocation, in disturbing the static balance of the colloids realizes a true physical heterogeneity of the constitutional albumins and proteins, which is equivalent to a sudden introduction of foreign proteins into the blood. According to others, cold effectively reduces the formation of the proteins modified by heterogeneity, the origin of which is chemical and no more physical: there exists a true urticaria to cold, of which the tests of passive transmission demonstrate the reality."

A series of experiences realized with the serum of those patients injected to healthy individuals and followed by an application of ethyl chloride on the points of injection shows that the hypersensitiveness to cold is easily transmissible. For the authors the transmissible hypersensitiveness to cold is not of urticarian origin and they conclude: "that hypersensitiveness can be compared with the hemoclastic crisis where cold, in certain conditions of terrain, produces a local vasomotor reaction and, on the other hand, a phenomenon of "shock" resulting from the hypersensitiveness of the organism towards the proteins modified by cold; in most of the cases the local vasomotor reaction is the only intervening factor to produce the eruption and the shock had no clinical expression."

Phlogogeneous and histaminolike substances. Dermographism according to some authors is the result of a local formation of a phlogogeneous substance, as in the eruption appearing after cold, this substance coming to formation locally and playing the *rôle* of an antigen, which, combined with the "anticorps" which give birth to an eruption. Still, Vallery-Radot believes this fact is not proven, and according to him, this substance would rather be liberated by the formation of rash, which, acting as an antigen would pass into the general circulation. With Lewis, histamine already in the skin of glucose, would be liberated under the influence of multiple factors increasing the permeability of the capillaries, so that "urticaria to cold depends upon the liberation of histamin-like substances under the influence of refrigeration." Vallery-Radot refuses such a theory, and, according to him, intermediate phenomenon would exist, unknown to us, and the liberation of this histaminolike substance could be incited by the stimulation of certain splanchnic fibres. But, there again, the question is in suspense.

Treatment. The treatment, according to Rouquès, is painstaking and dubious, because there is no consistent method of success, and one must procede by successive steps. With certain individuals, atropin and policarpin are successful, whereas daily injections of adrenalin during 20 days followed by ingestion of high doses of adrenalin have stopped some urticaria to cold. Adrenalin should be administered carefully on account of general reactions. Ephedrin is comparable with adrenalin. Other substances such as jaborandi, pilocarpin atropin and belladona give inconsistent results. Some authors have suggested repeated injections of histamin, which Vallery-Radot does not believe are justified. The action of histamin is little known, and its results contradictory.

Anticlasic therapy: calcium chloride by injection, autohemotherapy and Caesium eosinate have been advised, the latter substance having a preventive action against the accidents of shock.

The *leutic treatment* has given happy results in cases of heredo-syphilis; endocrine therapy gives satisfactory results.

On the other hand, *surgery* has published interesting results where urticaria *"a frigore"* was concerned; it disappeared after the operation of a big fibroma, or after appendectomy, both causes of irritation. Favorable cases have also been reported following abundant epistaxis or repeated bleedings.

Teau LeSage, Montreal.

DEROT, MAURICE.

Urticaria Due to Effort.

The author studies respectively: 1o. The leucocytic balance; 2o. The refractometric index of the serum; 3o. The acidobasic balance and the various humoral experimental and clinical reactions already reviewed, and concludes that "after an impartial study of the various case reports on urticaria due to effort, one is easily convinced with the fact that there is no unique pathogenesis of the phenomenon. Some individuals have a colloidoclastic diathesis and will show urticaria to effort, but have or will complain of attacks of asthma, spasmodic rhinitis, even or urticaria to food. In those individuals are to be found blood reactions and hemoclastic reactions preceding the eruption; in others, probably there is urticaria of humoral origin, possibly inherent to a specific hypersensitiveness towards desintegrated proteins produced by muscular effort."

"Other cases are concerned with nervous and irritable patients showing strong vasomotor reactions. In their past, no asthma, no spasmodic rhinitis is revealed, but the physical examination will show modifications of the vago-splanchnic reactions or endocrine troubles, such as thyrotoxicosis, so that the phenomenon of humoral "shock" are concomittent with or subsequent to the eruption, but do not procede it. Such individuals show no alimentary urticaria, but are whether exclusively sensitized to efforts, or to a certain extent sensitized to other physical agents, notably heat. Urticaria of a nervous origin is held responsible in such cases, implying an hyperreactivity of the cutaneous vasomotors. Urticaria to effort seems to establish a liaison between the two large classifications of urticaria due to anaphylaxy, and urticaria due to physical agents."

Teau LeSage, Montreal.

PASTEUR, VALLERY-RADOT AND PIERRE, BLAMOUTIER.

"Treatment of the Relapsing Urticaria."

Etiologic factors are multiple: effort, cold, digestive troubles, intestinal parasites, a determined food, endocrine troubles and the vago-splanchnic imbalance. The following methods are suggested: 1o. *Autohémotherapy;* 2o *Autoserotherapy.* In the former method, 5 to 6 c.c. of blood are injected every other day, and increased gradually, but not beyond 15 c.c., that is, 8 injections altogether. In the latter case, an intraveneous puncture will give a certain amount of blood, which is left to coagulate and to transudate at the temperature of the laboratory, then the serum is aspired and injected intravenously at the dose of ½ to 2 c.c. daily or every 2nd or 3rd day, in all, 10 to 12 injections.

3o. *Peptone injections.* The Witte peptone should be used, and the injections given subcutaneously every day or every other day: 2 to 5 c.c. of 5% solution; or, every day, an intradermic injection of 1/10 to 2/10 of a c.c., from a solution at 50%, should be given, although this method is inconsistent.

4o. *Sodium hyposulphite.* May be administered *per os* or intravenously. *Per os,* 4 to 15 grams per day, in a syrup of sugar—owing to the reducting power of the latter—may have successful effects according to this formula:

Syrup of sugar	25 grams
Sodium hyposulphite	
Distilled water	aa 125 grams

A tablespoonful before each meal is given the patient during 3 or 12 consecutive days according to his tolerance, as digestive troubles may appear with

high doses: diarrhea, sulphurated belching, etc.

The intravenous method is be st;then, the solution is at 20% in distilled or sterilized water. According to Ravaut, 2 c.c. are injected the 1st time and the doses progressively increased to 30 or 40 c.c., i.e. 6 to 8 grams of the salt. In severe cases, injections may be repeated daily, three a week being sufficient, in all 10 to 12 injections.

Magnesium hyposulphite at 10%, intramuscularly, has proved very successful in resistant urticaria.

Calcium salts, such as calcium chloride at the dose of 2 to 5 grams per day are used with success in daily routine. One might use: 1o. Calcium lactate in solutions at 8%; or 2o. Calcium chloride in a 10% solution: 5 to 15 c.c. every day or every other day intravenously. Transitory uneasiness is often noticed after the latter injection: intense sensation of heat, burning sensation of the face and extremities.

Calcium gluconate is used intramuscularly or intravenously.

It is recalled by the authors that, whatever drug be used, urticaria will prove a very sensitive humoral condition. Consequently, one must be very cautions and start with small doses, administering the injection very slowly. Never should intravenous injections of peptone be given to those patients. If an acidobasic imbalance of the blood is noticed, a high dose of phosphoric acid or of sodium bicarbonate, according to the condition of alkalosis or acidosis, should logically be given.

Splenic extracts have been used with success by certain authors, then a daily injection of 2 to 4 c.c. of pork splenic extract, or of calf splenic extract, corresponding to 25 grams of fresh liver, is well indicated.

Insulin has favorable results in certain cases, although the authors report entire failure, with their personal cases. Bleeding, in relapsing cases, has given satisfactory results. Diathermy, short-wave diathermy, sulphurated oil have been tried with various results.

To combat the neuro-vegetative excitability, "*gardenal*" or *luminal* might be used: 1 centigram every second hour, or intraveneous injections or sodium bromides at 10% in cases with violent pruritis.

Local treatment consists of keeping the diseased surface sheltered from air and friction, through the medium of ointments, pastes, liniments, etc. The following formula is advised by Darier:

Gelatine	15 grams
Glycerine	25 grams
Zinc oxide	15 grams
Water Q.S. for	100 grams

This glue is applied on the skin after liquefaction in bain-marie; then; while the substance is still sticky, the skin is covered with absorbant cotton strips, which have an adhesive action.

In conclusion: "treatment should not be carried through in a blind manner. The physician should, by a clinical study and biological examinations, strive to make out the cause of an urticaria. Only after such an investigation should the treatment be executed, and one would be especially indicated to counteract a harmful action producing the relapses of urticaria."

This monography is concluded by a study of *Urticaria and the Thermal Cure of Vichy*, by A. Mathieu de Fossey.

Teau LeSage, Montreal.

ABDOMINAL SURGERY

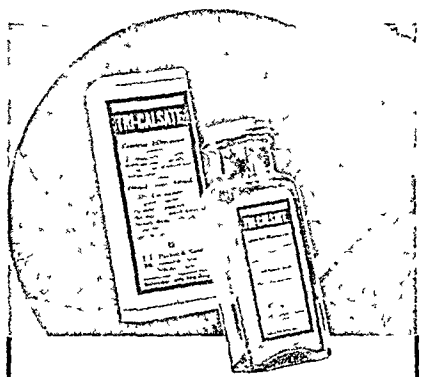
HINMAN, F.

A Simple Seven Suture Method of Bilateral Uretero-Intestinal Implantation. Report of 12 cases. S. G. O., Vol. 61, No. 6, pp. 802-815, Dec., 1935.

The author describes a simple seven suture method of uretero-intestinal implantation in which the probe and cautery are used. Considerable precision of execution and careful preparation of the patient are necessary.

The patient should have been on a non-residue diet for three days preceding operation. Castor oil and enemas are used to empty the intestinal tract. Through a low mid-line abdominal incision the peritoneum is incised as near the pelvic colon as possible alongside that portion into which the ureter is to be implanted. The peritoneum is now dissected away laterally elevating the ureter with it. The ureter should be carefully dissected free from that flap of peritoneum down to the juxta vesical portion which is doubly clamped, cut and ligated. The ureter on the opposite side is now prepared in the same manner and the exact sites of the implantations decided upon. The new relations must be studied carefully and a point neither too near nor too far away chosen for the point of implantation.

After the site of implantation has been decided upon it should be marked by two stay sutures. The incision in the bowel wall should be a clean cut 2.5 to 3. centimeters long between these sutures; it should extend down to but not through the submucosa and its blood vessels. The muscle and peritoneum are gently teased back and the ureter sutured to the submucosa by means of 20 day four 0 chromic catgut on a one-half circle plastic atraumatic needle. The first three sutures are placed so as to form an isosocles triangle in the submucosa. They are placed on each side of the ureter and at a point on its anterior surface; none of them are tied at this time. The ureter is incised at a point distal to the site of implantation and a probe passed into its ligated end. The three sutures are now used to elevate and hold the triangle of submucosa which is pierced with an electro cautery. The ligated



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end of the ureter is now pushed through that opening and hangs in the lumen of the bowel. The incision in the submucosa must be neither too short nor too long; it must be just the right length. Sutures No. 4 and No. 5 are used to anchor the ureter in the upper part of the muscular channel. Sutures No. 6 and No. 7 are of intestinal linen or intestinal silk. They close the lower part of the incision over the point where the ureter penetrates the submucosa. The peritoneal flap is now sutured to the bowel medial to the implantation thereby extraperitonealizing it. The opposite ureter is treated in the same manner but at a point higher or lower on the bowel. The abdomen is closed without drainage.

In the twelve cases in which the author has performed this operation *none of them developed complications* directly attributable to faulty implantation.

Twenty-eight figures accompany the article.

Nelson M. Percy, Chicago.

HAYMOND, H. E.

Massive Resection of the Small Intestine. S. G. O., Vol. 61, No. 5, pp. 693-705, Nov., 1935.

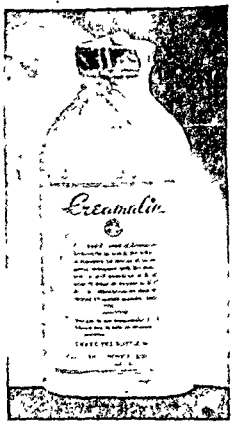
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the more important conditions necessitating extensive resections were: Volvulus—76 cases; Strangulated Hernia—45 cases; Mesenteric Thrombosis—34 cases; Female pelvic disease—21 cases. Abdominal injuries and tuberculosis of the small intestine accounted for 16 cases each.

The age incidence was from 8 to 76 years. There were 156 males and 75 females. Mortality was highest in the cases in which greater lengths of intestine were resected. The operations including lateral anastomosis were the most successful.

Studies made on a number of patients who recovered showed a definite abnormal loss of nitrogen and an excess of fat in the stool. In one of the author's cases in which only 55 centimeters of small bowel remained the blood chlorides, non-protein nitrogen, carbon dioxide combining power and hydrogen ion concentration were found to be within normal limits.

Diarrhea was the most prominent and most disturbing post-operative complication in all the surviving cases. That diarrhea cannot be controlled by drugs. The patients fare best on a fat poor, protein adequate and carbohydrate rich diet.

The author reports three cases of massive resection of the small intestine. Seven tables and a very large bibliography accompany the article.

Nelson M. Percy, Chicago.

JORDAN, FERDINAND M.

"Clinical Aspects of Gastrojejunal Ulcer." Amer. Jour. of Surg., (New Series), 31:83-87, Jan., 1936.

The incidence of gastrojejunal ulcer is rather difficult to estimate, varying in different reports from 1.6 per cent to 34 per cent. Perhaps about 10 per cent would be a fairly accurate average. The appearance time of the symptoms after gastro-enterostomy is much more definite—in most cases less than a year, ranging from then until as late as nineteen years and averaging perhaps about four and a half years. It is far more likely to occur when the primary operation is performed for duodenal ulcer than when it is done for gastric ulcer. Males and nervous high-strung individuals are more commonly affected. Neglected foci of infection are definite etiological factors. High gastric acidity also contributes to the likelihood of gastrojejunal ulcer.

The symptomatology in uncomplicated cases is fairly definite. There is a recurrence of the previous symptoms with this important difference—there is usually a change in the location of the pain which in most instances is farther to the left and lower in the abdomen than previously. Vomiting frequently accompanies the pain and hemorrhage is more common. This latter symptom is especially important if the original ulcer was non-hemorrhagic. The re-

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are conditions in the correction of which a free flow of bile is essential. For nearly 25 years the medical profession has stimulated bile secretion by administering

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sponse to medical ulcer management may aid in establishing the diagnosis. Roentgenologic evidence may be confusing because of the large proportion of false negative findings. Criteria relied upon are (a) the presence of a niche; (2) persistent deformity at the stoma or of the stomach or jejunum in the region of the stoma; (c) the presence of a gastrojejunocolic fistula; and (d) closure of the stoma. The condition must be differentiated from a reactivation of the original ulcer, malfunctioning gastro-enterostomy, nervous dyspepsia, and diseases of other structures. The presence of hemorrhage, perforation, or a gastro-jejuno-colic fistula adds to the difficulty of diagnosis.

Proper medical and dietary management after the first operation, and elimination of possible foci of infection may lower the incidence of this condition. The author does not favor the substitution of partial gastrectomy for gastro-enterostomy as a prophylactic measure, since that operation has a higher average mortality than the average risk of gastrojejunal ulcer after gastro-enterostomy. However, when the ulcer actually appears, partial gastrectomy is probably the operation of choice. Sometimes simple disconnection of the previous gastro-enterostomy may suffice. Medical treatment, alone, is not satisfactory.

J. Duffy Hancock, Louisville

CORFF, MEYER.

"Acute Perforated Peptic Ulcer—(A Review of Sixty-three Cases)" Amer. Jour. Surg., (New Series), 31:77-83, Jan., 1936.

In the series of cases reviewed, the author observed the characteristic sudden onset of extremely severe pain in the mid-epigastrium, accompanied by board-like rigidity of the entire abdomen. The rather pathognomonic sign of obliteration of liver dullness with elevation of the diaphragm, due to free gas in the peritoneal cavity, was not so constant as frequently reported. Eighty-five per cent of the cases gave a history of hunger pain and food relief for a year or more. The only premonitory symptom was the failure to obtain the usual food relief of the pain. The average age of the patients was thirty-seven, practically all were males, and the duodenal ulcers outnumbered the gastric five to one. The operative mortality was 25.8 per cent which is about the average.

Different types of operations were performed, several different anesthetic measures were employed, and the use of drains was varied. In this series, it appeared that the lowest mortality was obtained when simple suture of the perforation was done under spinal anesthesia and drainage instituted to the ulcer area, the pelvis, or both places. Continuous post-operative gastric drainage by the Wangensteen method was employed in all the cases. However, the greatest factor in mortality was the length of time between perforation and operation. That this is a matter of hours is clearly shown by the fact that the average time for those who lived was nine and one-half hours, for those who died thirteen and one-half hours

J. Duffy Hancock, Louisville.

M. BRUN (Blois).

Surgical Indications in the Treatment of Pelvic Ulcer, (or Gastro-Duodenal Ulcers). (Les indications chirurgicales dans le traitement des ulcères gastro-duodénaux). Gaz. Méd. de France et des pays de Langue fr., No. 15, pp 715-17, Sept., 1935.

Gastric surgery, and especially simple gastro-enterostomy, is not at the present time a procedure of great danger. The obscure etiology of ulcer and the frequent recurrences still often justify surgical treatment. Medical and surgical treatments keep, however, their respective indications:

(1). In which cases is it necessary to intervene surgically? This question is a general one. (2). Being given these cases, which kind of intervention shall



The prescorbutic state, subclinical scurvy, is much more common than was formerly supposed. This diagnosis should be considered as the constitutional basis for obscure cases of gingivitis, dental caries, anemic states, certain allergic skin and intestinal phenomena, and recurring infections.

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CANNED FOODS AND THE PUBLIC HEALTH

IV. BOTULISM

o Several of our readers have inquired as to the possibility of botulism resulting from the consumption of commercially canned foods. The canning industry is proud of the part it has played in the eradication from its products of this deadly type of food intoxication. We are glad to devote this space to a discussion of this important topic.

During recent years, the daily press periodically carries reports relating how one or more members of a family, or of a group of persons, were stricken after a meal, usually with fatal results. Sometimes these accounts describe how an "anti-toxin" was rushed to the scene—an indication that botulism was involved. These press reports often include the statement that a "canned food" was incriminated as the cause of the illness.

We wish to emphasize that as far as the records go, these outbreaks without exception are not attributed to foods commercially canned in this country. In practically every instance, it was found that the foods —usually of a non-acid or semi-acid nature —had been preserved at home by the use of inadequate heat sterilization processes (1). These press reports, by not stating correctly the type of food involved, have done much to cast unwarranted suspicion on commercially canned foods as possible causes of botulism.

Botulism, or acute toxemia due to clostridium botulinum, is by no means a new affliction. As early as 1802—ninety-five years before van Ermengem discovered the true cause of the intoxication—warnings were issued against botulism. However, not until severe outbreaks occurred in this country some fifteen years ago, was it realized that cognizance should be taken of the fact that foods canned by the methods used in those days could become contaminated with the toxin of this organism. This fact having been realized, the canning industry took immediate steps to prevent such contamination of their products.

Research was inaugurated and has been continued to which the industry has contributed not only financially, but also by the studies of scientists associated directly with the canning industry (2). The end result of these researches was the development of scientific methods of determination of heat sterilization treatments, or heat processes as they are known to the industry, which would be adequate to insure the safety of canned foods from the standpoint of botulism (3).

The effectiveness of the measures generally adopted by the canning industry of the United States is evidenced by the fact that no case of botulism attributable to an American commercially canned food has occurred during the past ten years (1a). Foods packed in commercial canneries are heat processed not only to insure protection from bacterial spoilage causing merely the loss of the food, but to render them safe from the standpoint of botulism, as well. In fact, a sterilizing process sufficient to insure the destruction of the most heat resistant strain of Cl. botulinum ever isolated is considered the minimum requirement of heat treatment of commercially canned foods. The National Canners Association has issued lists of scientifically determined processes for non-acid canned foods with which canners comply (4).

Such are the facts. The American canning industry offers its products to the consuming public for what they are: namely, wholesome and nutritious foods.

AMERICAN CAN COMPANY

230 Park Avenue, New York City

1. a) *1935 Amer J. Public Health*, 25, 201 b) *1935 J Amer. Diet. Assn* 11, 18
2. *1916 J Bacteriology* 31, No 1 P. 71 *1921 Amer J Public Health*, 13, 108 *1923 J Inf Dis* 31 650
3. *1923* Natl Res Council Bulletin, 7, No 37
4. *1931* N C.A Bulletin 26 L, Revised

This is the twelfth in a series of monthly articles, which will summarize, for your convenience, the conclusions about canned foods which authorities in nutritional research have reached. We want to make this series valuable to you, and so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles.

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be used? This is a purely surgical question.

In answer to "1": chronic ulcer belongs more to surgery than does acute ulcer, which may not recur if well treated medically. The absolute indications of surgery are: pyloric stenosis, perforation, serious hemorrhage. In these cases, surgery is imperative, the question here being one of opportuneness and of choice of method.

Relative surgical indications are painful ulcer, chronic ulcer, non-response to medical treatment and secondary anemia (hemorrhagic ulcer).

In answer to "2": What method to employ? In the non-complicated gastro-duodenal ulcer: whether to use gastro-enterostomy or extensive gastrectomy?

Gastro-enterostomy is marvellous in pre-pyloric ulcers with spasmodic stenosis and hypersecretion and in certain small ulcers of the lesser curvature. Gastroectomy is indicated in the large chronic prepyloric ulcers where malignant change is suspected; in the hard callous type of ulcer of the lesser curvature; of the old ulcer of the body of the stomach in which the base is formed by the liver or pancreas. In the ulcers placed near the cardia extensive gastrectomy is dangerous. Subtotal gastrectomy is often possible. Palliative operations are more often to be recommended such as transpyloric gastrostomy or jejunostomy.

For duodenal ulcers, experience commends simple gastro-enterostomy, if excision of the ulcer and suture of the duodenum do not seem to be of easy accomplishment.

Pierre Smith and Thomas Farmer,
Montreal, Canada

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E STARR JUDD AND M. TISCHER HOFFNER, M.D.

Jejunal Ulcer. Ann. Surg., Vol. 102, No. 6, Dec., 1934.

The authors briefly review the statistics prepared by Paterson who found the incidence of jejunal ulcer to be 2.4 per cent in a series of 495 operations; and of Moynihan who reports an incidence of 1.6 per cent in a series of 613 patients who underwent gastrojejunostomy. The occurrence of the lesion varied between 1.2 and 3.2 per cent in the two series of cases published by Walton in which gastrojejunostomy was employed for duodenal ulcer. Wright reported 6 per cent while Wilkie's statistics revealed an incidence of 3.5 per cent. Heuer drawing his conclusions from his own experiences and from published reports of those of other authors says that the results of 17 authors from various countries show that recurrent or jejunal ulcer follows gastro-enterostomy in from 0.9 to 6.9 per cent of the cases, the average incidence being 3 per cent. He found that the statistics given by eight authors showed that recurrent or jejunal ulcer follows partial gastrectomy in from 0.6 to 6 per cent of cases, or an average of 1.9 per cent. This somewhat lowered incidence has been reported by many men but the authors of this paper feel that although jejunal ulcer occurs less frequently after partial gastrectomy, the operative mortality in such a procedure, when used routinely, will more than offset the increased liability to recurrent ulceration after conservative operations.

From 1906 to 1931 gastrojejunostomy has been carried out at the Mayo Clinic in 10,388 cases in the treatment of duodenal ulcer—of that number there were 251 patients who developed proven jejunal ulcer subsequent to their gastrojejunostomy which was performed at the clinic. Thus the authors report an incidence of 2.4 per cent and in the rest of their paper discuss these

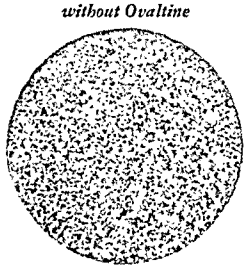
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cases and the problem of jejunal ulcer as to etiology, pathology, symptoms and treatment.

In classifying their cases as to age and sex, they find that the highest incidence of recurrent ulcer occurred during the third and fourth decades and that males seem to be more susceptible than females, for the proportion is at least 4 to 1 for primary ulcer, and approximately 13 to 1 for jejunal ulcer.

Jejunal ulcer may be considered, in the light of the authors findings, as a complication limited primarily to cases of duodenal ulcer in the treatment of which the jejunum has been anastamosed to the stomach, since in this series of 597 patients there were only 20 cases in which the original lesion was a gastric ulcer.

The etiology of this condition is discussed at length but the etiology remains unknown. The much discussed theories of the causation of jejunal ulcer are mentioned, among them being that of hyperchlorhydria which has perhaps the widest acceptance. The role of infection in the formation of an anastamotic ulcer is presented and the frequency with which gastritis and jejunitis is associated with these lesions is emphasized by some authors. It was formerly thought that the use of unabsorbable suture material contributed to the formation of jejunal ulcerations but this factor is ruled out by the authors who state that at the Mayo Clinic unabsorbable suture material is only very rarely used in their gastrojejunostomies.

Some of the various errors of technic which have been suggested are: (1) Too small an opening in the anastamosis; (2) Placing the stoma too high on the stomach; (3) Inclusion of inflamed gastric mucosa in the anastamosis; (4) Formation of a spur by redundant mucous membrane; (5) Invagination of the jejunum into the stomach; (6) Failure to approximate mucous membrane to mucous membrane; (7) Kinking of the distal loop; (8) Formation of a hematoma. While all of these factors must be considered and then eliminated in order to obtain satisfactory results from the operation, they do not in themselves constitute the entire answer to the problem.

The authors found that 90 per cent of the jejunal ulcers were single and that 48 per cent were situated in the line of the anastamosis. Their characteristics are similar to those ordinarily observed in peptic ulcer. If the lesion is acute the walls are soft and there is danger of perforation. However, the chronic type has thick, calloused walls and frequently has a deep crater. Owing to the proximity of the colon, it is particularly vulnerable, and if the penetrating tendency continues, a gastrojejuno colic fistula may develop as in 8.7 per cent of these cases reported.

The symptoms and signs which the authors feel are of diagnostic importance are: (1) The recurrence of pain similar though often more severe than that of the original ulcer; (2) Gastric hemorrhage, especially in the absence of bleeding before the primary operation; (3) Gross gastric retention; (4) Gastrojejunocolic fistula with its attendant symptoms, i.e. passage of watery, fatty stools, belching of gas with fecal odor, fecal vomiting, rapid loss of weight; (5) Progressive course and lack of satisfactory response to medical treatment.

In discussing the treatment of jejunal ulcer the authors first deal with the preventive treatment and state that the most effective means of preventing jejunal ulceration after the surgical treatment of peptic ulcer is to avoid gastrojejunal anastamosis in cases in

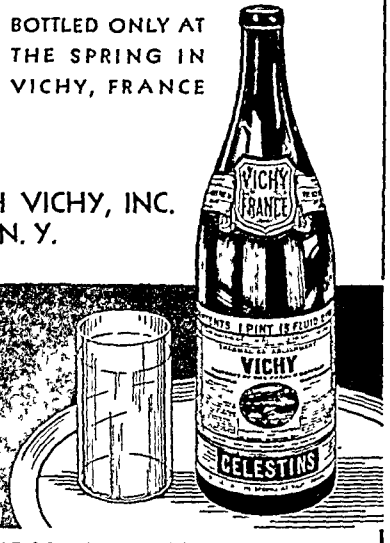
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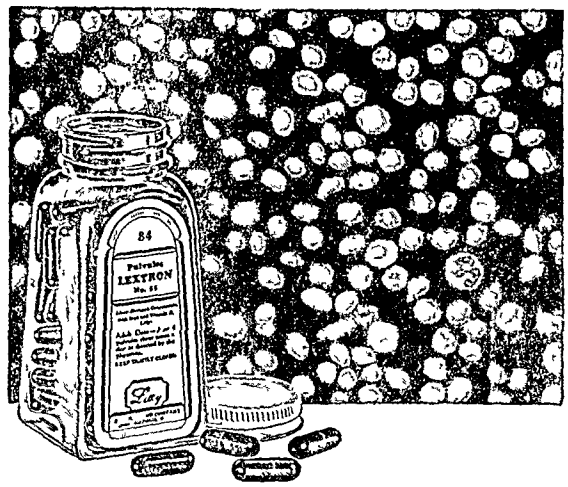
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which gastric acids are high and little or no pyloric obstruction exists. "We now know that jejunal ulcer is likely to occur in individuals of this type, particularly if they are young and of a nervous high-strung temperament. Consequently, if surgical treatment of a peptic lesion becomes necessary in such cases, it is preferable to carry out some form of local operation on the duodenum and maintain normal gastrointestinal continuity whenever it can be done. For this purpose, excellent results have been obtained from excision of the lesion, together with the anterior 2/3 of the pyloric sphincter muscle, with closure as a gastro-duodenostomy. Gastrojejunostomy still constitutes an excellent form of treatment for peptic ulcer, however, for not only is the mortality low, but there is an excellent chance of cure, as 86 to 88% of the patients so treated obtain satisfactory results.

As regards the choice of operation for jejunal ulcer—the authors feel that if the primary ulcer in the stomach or duodenum has healed and the pylorus is unobstructed, the most judicious procedure may be to disconnect the gastrojejunal anastamosis and excise the jejunal ulcer. In other cases of jejunal ulcer following gastrojejunostomy, they feel that one of the following operative procedures may solve the problem: (1) Disconnection of the gastrojejunal anastomosis, resection of the jejunal ulcer, and pyloroplasty or gastro-duodenostomy; (2) Disconnection of the gastrojejunal anastomosis, excision of the jejunal ulcer and gastric resection according to the Bilroth I method; (3) Gastric resection at the level of the previous gastrojejunal anastomosis with a Polya type of reconstruction. Occasionally jejunostomy may be used to advantage either alone or in conjunction with any of the other procedures, and if patients condition is such that an extensive operation is contraindicated, simple jejunostomy may put the upper gastro-intestinal tract at complete rest until the acute phase of the disease has subsided.

Only 6 per cent of the 597 patients traced required a secondary operation for jejunal ulcer, regardless of the variations in the nature and extent of the primary surgical treatment of the jejunal lesion; however, the authors emphasize the fact that a person in whom jejunal ulcer develops very likely has a high ulcer potentiality and so should be advised to adhere to a regulated diet indefinitely and to return at intervals for a review of his condition.

Charles T. Sturgeon, Los Angeles



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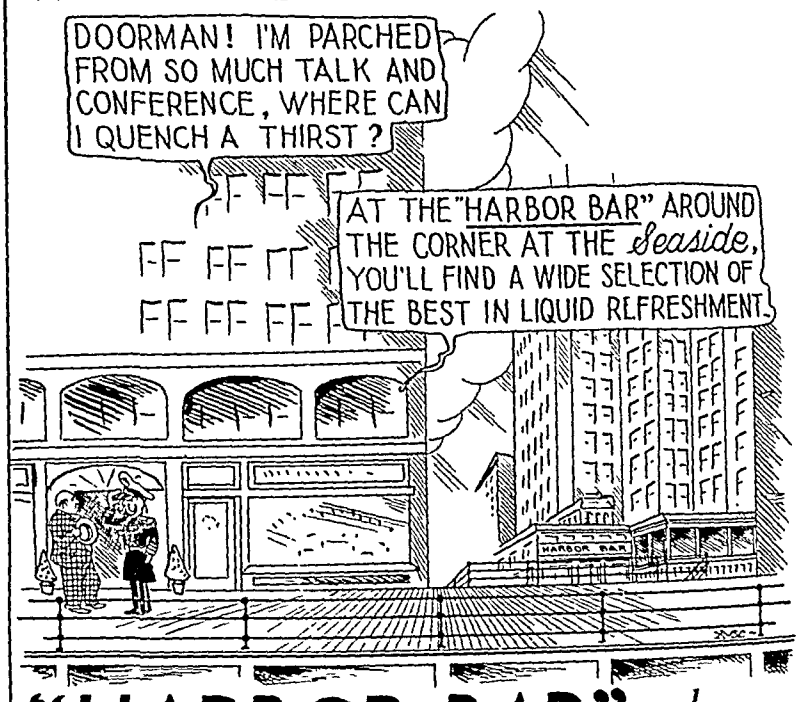
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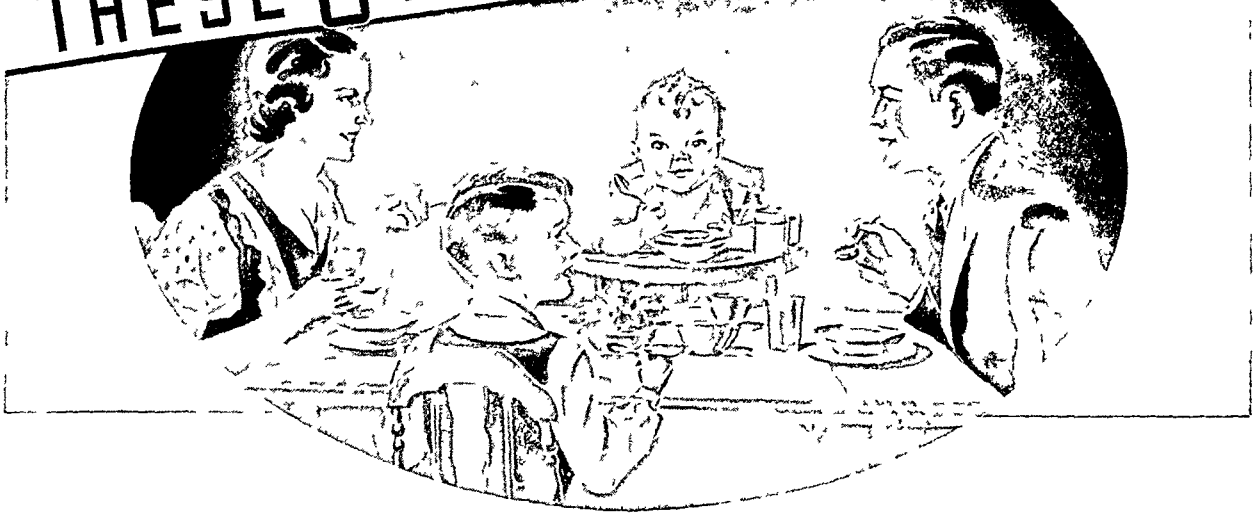
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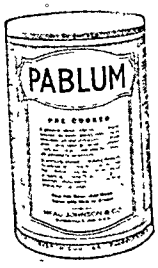


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SECTION I—*Clinical Medicine: Diseases of Digestion*

The Significance of Chronic Gastritis

By

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ST. LOUIS, MISSOURI

GASTRITIS is given a prominent place in the recent studies of the causes of several diseases, and an additional attempt at an appreciation of its actual significance seems permissible. The clinical diagnosis of chronic gastritis falls into that category of things, the affirmation of which places the burden of proof upon the skeptic. Because of repeated citation, the precursory and causal relationship of chronic gastritis to other gastric diseases is coming to be regarded as established, although the facts do not warrant such categorical conclusions. In practice, the clinical diagnosis of chronic gastritis is often inferred in the reverse direction rather than demonstrated objectively. It is insufficient to assume that, because of association, gastritis has been the cause of localized organic changes, and also, because of the suppression of secretory function, that this results from gastritis.

Any search for a common denominator is always fascinating. The discovery of a factor common to several disease entities would be a boon to preventive medicine. Hurst (1) recently said, in concluding a lecture on "Achlorhydria": "I expect that this is the last time there will be a discussion on achlorhydria, for the problem has shifted, and we must in future discuss gastritis, its causation, early diagnosis, treatment and prophylaxis, just as we discuss nephritis rather than albuminuria. It is gastritis which causes achlorhydria, and gastritis, not achlorhydria, which causes Addison's anaemia, sub-acute combined degeneration of the cord and predisposes to carcinoma of the stomach. The prophylaxis of gastritis is the prophylaxis of these diseases."

Gastritis has been demonstrated in surgical material in an almost constant association with gastric cancer and with gastric, duodenal and stomal peptic ulcers. It is also assumed and affirmed that gastritis is the underlying condition of gastric hyperacidity and of gastric anacidity. Gastric hyperacidity may have an associated erythrocythemia; achlorhydria is an almost constant accompaniment of the non-hemorrhagic anemias, and frequently it has as a sequel morning diarrhea, which may be promptly corrected by the administration of hydrochloric acid. These relationships of gastritis to other intrinsic gastric pathology, to extragastro-intestinal conditions and to systemic disease give the problem of its possible causal relationship great importance.

The generic term 'gastritis' has been loosely used and the pathological implication of the undefined term is not always clear. Its adjective qualification upon the morphologic, functional, etiologic and clinical attributes is so multiple and varied that the consequent ambiguity shows the general inadequacy of our understanding of the condition. The term is defined, however, in reference to the operative findings associated with cancer and ulcer, by description of an oedematous, reddened mucosa which microscopically has round cell infiltration involving the lymph follicles, and also an increase of the goblet cells. Submucus diapedesis of red cells and mucosal erosions may be present. Although in general discussions it is not often made clear, an atrophic type of gastritis is found in cases without cancer which clinically have shown an achlorhydria, often associated with anemia. It is not apparent that this is or is not a later stage of the follicular type of gastritis. In other discussions, the term is loosely used. It is definitely stated that gastritis denotes, not a superficial catarrhal inflammation from direct irritation, but a disease of the glandular parenchyma caused by circulating toxins. These broad pathological connotations of the term give rise to much confusion. The pathological changes and the clinical picture of disease are not static, and remote antecedents and relations are difficult to determine. The findings of gastritis, upon which the premise of an etiological relationship is based, are late pathological data and generally lack the adequate previous clinical evidence necessary to indicate the existence of the gastritis prior to the various associated diseases.

Due to these considerations, the *clinical diagnosis of gastritis* is receiving renewed and increased interest. The roentgenological study of the mucosa by its "relief" patterns, and the gastroscopic inspection of the mucosal surfaces are the chief methods of direct examination which have been recently developed. Other than these methods, the medical history, which is exceedingly ambiguous, the findings at gastric aspiration, and the thoughtful elimination of other disease form the not too-secure foundation for the clinical diagnosis of chronic gastritis. Although a deficiency of gastric juice is the most important functional finding in gastritis, it is in no sense pathognomonic. Even the diagnosis of acute gastritis depends largely upon

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the positive clinical history of injurious ingestion and of the immediate revolt of the stomach. There is no clinical method of diagnosis which can, with certainty, indicate the extent, degree, or kind of mucosal inflammation by which the actual fundamental pathology may be known prior to direct study of operative or autopsy material. Eusterman (2) says, "personally, I would not like to make a diagnosis of gastritis in one of its various forms without either gastroscopic or roentgenoscopic confirmation and apparently only the hypertrophic forms of gastritis can be recognized by the latter procedure." On the other hand, others find that the clinical diagnosis is easily made by gastric lavage. It is apparent that there is no clinical method by which effectively to follow these associated "diseases" and to demonstrate with finality their pathological association or disassociation during their evolution.

Is *gastritis a causative factor* in gastric ulcer and in what manner could it be an etiological factor in duodenal ulcer? Konjetzny, Stoerk, Puhl, Bohmausson and others believe that gastritis precedes and is to be found in all cases of chronic peptic ulcer, and bring evidence to show that such lesions, existing even in the absence of ulcer-formation may give rise to symptoms typical of ulcer (3). Overgaard (4) finds that "on the basis of reports from numerous authors, it must be accepted as certain that the antrum gastritis with its accompanying acute and chronic changes forms the foundation on which typical ulcer develops." Johnston (5) finds, as previously recorded by Orator, etc., that, of surgically resected stomachs, there are approximately two-thirds exhibiting chronic follicular gastritis and one-third with simple chronic gastritis. "Follicular gastritis" (37) was recorded as associated with duodenal ulcer (18) two and one-half times as frequently as with gastric ulcer (8), not including stomal ulcers (4), and six times as frequently with gastric cancer. In four cases, no localized lesion was present. Simple chronic gastritis (18) was associated with duodenal ulcer (7) one and three-fourths times as frequently as with gastric ulcer (4), not including stomal ulcer (1) and two and one-third times as frequently with gastric cancer. In three cases, no localized lesion was found. No note is made of the pre-operative function of the stomach, that is, of gastric motility and gastric secretion. It may be suggested that impairment of motility and prolonged retention of secretions with the continuous gastric activity involved can well be, in this type of gastritis, the factor which is common to all the cases, even those in which no localized lesion was found. It is probable that the simple chronic gastritis merely is an earlier phase of a gastritis which later becomes chronic and follicular. The predominance of duodenal ulcer over gastric ulcer cannot be reconciled to the broad assertion of causal relationship when the reports consistently record gastritis with it as with gastric ulcer. If the anatomical pathology of gastritis is a causative factor in gastric ulcer, then gastric ulcer and gastritis should have a typical and inclusive association.

To further discuss this problem, a definition of peptic ulcer is necessary. The disease of peptic ulcer is fundamentally an alteration of the function of the gastro-duodenal segment into an unphysiological status which permits the development of and, by continuance, maintains the localized round ulcer lesion which is in fact only one of the abnormalities of the entire disease syndrome. The ulcer lesion is the end result of intralumenal chemical conditions produced by multiple and varied factors which allow, at the site of some injury which otherwise would heal promptly, the progressive localized destructive excavation of the wall of the stomach by necrosis and digestion. Thus is created, according to location, either duodenal ulcer or gastric ulcer. The lesion occurs and continues by reason of interference with the native healing resident in these tissues. Healing is prevented because of the prolonged digestive activity during the abnormally lengthened digestive phase which has become disproportionate to the reduced or absent quiescent phase of gastric function. Healing of the lesion is effected when the prolonged chemical processes are successfully restricted to their normal physiological period and cure of the disease is attained when the normal interdigestive phase of gastric function is restored. The fallacy of the conception that the primary agent or reason for the break in the continuity of the mucosa is also the reason for the continuance and extension of the ulcer lesion has impeded the understanding of other factors and misdirected efforts of both medical and surgical therapy.

With the premises of an acid-pepsin genesis of peptic ulcer, gastritis might be considered to operate by providing the stage-setting of gastric ulcer by reason either of hypersecretion or of the gastroparesis, which usually accompanies, and the resulting abnormal lengthening of the time-factor of active acidity. Gastritis may also be conceived to be the essential injury to the tissue which precedes the excavating processes. These possibilities presume that the gastritis is prodromal, which however, is not proved. There is often an inference that the usual hypochlorhydria of gastric ulcer is an evidence of gastritis, rather than being merely an expression of the hypotonicity of the stomach. Johnson admits the possibility that chronic follicular gastritis may exist without ulceration but is inclined to believe that it may have an etiological relation to the peptic ulcer. Arafa notes a few cases of pyloric gastritis and duodenitis which were operated upon because the symptoms were precisely similar to those of ulcer. On the other hand, Hurst (6) finds that "chronic gastritis is a comparatively common condition with a fairly definite clinical picture and a very characteristic test meal, but in my (Hurst's) experience it is rarely associated with symptoms or signs of acute or chronic gastric or duodenal ulcer."

I can find no significance in the fact that chronic follicular gastritis gives the symptoms and many of the signs of chronic ulcer, as has been emphasized by Fitzgerald (7). Except for the pain of the actual lesion or of its peritoneal extension, the symptoms and signs come from the functional impairment and derangement, and take place because it is the same organ that is impaired rather than that the diseases are necessarily etiologically related. Henning (8) has said "that so-called 'ulcer complaints' are in no way pathognomonic of ulcer." He also finds that gross bleeding occurs without ulcer as frequently as from ulcer and tumors. It has not been my experience to meet with non-ulcer gastric hemorrhage which could be explained on a gastritic basis.

If gastritis supplies the tissue injury from which excavating ulcer evolves, it is strange that duodenal ulcer exists more frequently than gastric ulcer, even

among the advanced cases of ulcer represented by the surgical material studied. That a duodenitis analogous to the gastritis is associated with duodenal ulcer, does not solve the dilemma.

It appears, if we accept the theory of the acid or peptic genesis of ulcer, that functional change extends the time of active secretion and abolishes the interdigestive rest period, which is recuperative and reparative. This is all important. Gastritis may well result from this constant presence of effective gastric juice, but the absence of gastric ulcer in so many instances of gastritis seems to point at least to the necessity of an additional accessory factor for ulcer initiation, otherwise there would be found in the material reported more gastric than duodenal ulcers.

Gastritis of various types has a frequent association with *cancer of the stomach* and that is the best support given for the hypothesis that gastritis is an essential precursor to cancer. Polland and Bloomfield (9) find that anacidity in cancer of the stomach is associated with a chronic gastritis antecedent to the growth and Bloomfield (10) states that "cancer tends to develop in stomachs already the seat of chronic gastritis with anacidity." In support of the hypothesis of an inflammatory basis for cancer, it is also asserted in analogy that chronic mastitis and glossitis precede carcinoma of the breast and tongue respectively, which statement may well be challenged. The characteristic short history of primary gastric cancer must indicate that any preceding gastritis has been asymptomatic, and it is also asserted as a fact, but without demonstrated basis, that gastritis for a long time may be asymptomatic. The reported high percentages of gastritis found with cancer can mean as yet only the coordinate association of the two diseases. Certainly, any logical deductions from established facts could indicate only that the functional disturbances of cancer are more pertinent causes for gastritis rather than is the reverse. Both the acid and anacid varieties of gastritis are prevalent disproportionately to their association with cancer in any causal relationship. Even a long clinical history of dyspepsia cannot alone support the presumption of gastritis, for generally dyspeptic symptoms arise more often from intestinal than from primary gastric conditions. Certainly, in view of the many exceptions, cancer cannot be asserted, on the basis of the rare actually observed sequence, to be a liability of gastritis of any type.

Danger arises in practice not from the certainty or likelihood of any sequence in pathology but from the very great difficulty in the clinical differentiation of the nature of prepyloric pathology as between gastritis, benign ulcer and cancer, and the frequent suggestions in prominent places of radical surgery for these cases should be correctly and frankly based upon the uncertainties of diagnosis rather than upon presumptions of any sequence in pathology. The type of gastritis associated with cancer *per se* or with the several types of cancer has no constancy. Chronic productive, interstitial gastritis with atrophy is more frequent; hypertrophic gastritis is found in some cases of adeno-carcinoma (11). It is said that gastric atrophy occurs with carcinoma of other organs through a deleterious influence on the organism as a whole. However, statistics of achlorhydria fail to show any greater increase in its incidence with age, in association with extra-gastric disease or in otherwise healthy people (12). Ewing (11) states that "the inflammatory reaction frequently meets the invasion of tumor cells. It is a highly significant feature of malignant tumor growth and must be regarded as a defensive process." This direct reaction to tumor growth must not, however, be confused with the wider mucosal inflammation which is denoted by the term 'chronic gastritis.'

In what manner may gastritis be conceived as a change precursory to malignancy of the mucosal cells? Recourse to the time-honored theory of "chronic irritation" as a cause must be used unless the direct effects of inflammation are considered a stimulus which will cause cell division to escape physiological bounds. The idea of chronic irritation may, in argument, be rationalized to indicate any form of foreign physical, chemical or bacterial action, but it has doubtless been used commonly in the sense of mechanical excitation. If the conception is, however, broadened to include any continuing stimulus to increased metabolism in the mucosal cells, it will still fail to sustain an etiological relationship which would support the precursory position of gastritis to cancer. As long as we have no recurring observations of evidence of the transition of ordinary gastritis into cancer, the significance of the gastritis as a cause of cancer is wholly unproven. The assumption that long standing achylia is an indication of gastritis helps little, for the known cases of cancer occurring after years of achylia are so rare that, considering the frequency of both diseases, their coincidence can indicate no pathological relationship.

Erskin (13) has examined the conception of irritation as the cause of cancer and cannot find support for it in known facts. He says that "if the irritation theory is to be considered tenable, the incidence of cancer should conform to three postulates: (1), Cancer should develop most frequently upon irritated areas; (2), Chronic irritation should be followed by the appearance of cancer; (3), Cancer should not appear on unirritated areas."

The assumption that tar acts merely as a chronic irritant, continued application of which causes the tissue to be the subject of malignant change, is brought into doubt by the fact that only those tars which contain carcinogenic hydrocarbons have this capacity. Further, Cook and Dodds (14) demonstrated that these hydrocarbons have also an estrogenic action. This indication that the carcinogenic effect arrives from a specific stimulus characteristic of certain molecular structures, compels the conception that for chronic irritation to be productive of cancer, it must at least develop in the tissues such a specific agent. With relation to skin cancer, Somerford (15) says "the ideal method of preventing cancer in industrial workers should be beyond the control of the workers, and among oil workers it is possible now to supply oil possessed of oil-lubricating properties without any of the carcinogenic constituents."

Macklin (16) in an excellent report of statistical analyses of clinical material gives all but conclusive support to the hereditary nature of cancer. She says: "the medical profession has laid so much stress upon chronic irritation as a factor, that it neglects the evidence of inheritance which lies before it." She, however, undoubtedly believes that an acquired disease may precipitate an hereditary one for she does not wholly dismiss the idea of chronic irritation but states further that "chronic irritation undoubtedly plays a rôle in the production of some cancers. In others it is

absent. It speeds up a reaction that is already present, to take place sooner than it would have done without the stimulus of injury." A factor of acceleration is however, not causal. On the experimental side of cancer study, Maude Slye's work is conclusive of the hereditary transmission of cancer in animals in spite of any argument whether it may be by a recessive or a dominant factor. The question of the relationship of an hereditary factor and an acquired inflammation to a precancerous condition is also present in any polyposis of the mucous membrane. It is stated by Ewing (11) that polyposis is a "feature of the late stages of catarrhal inflammation of these tissues." It is more readily conceived how a diffuse inflammation would effect an extensive diffuse polypoid hyperplasia of the affected mucosa than that it would cause a neoplasm of localized origin.

Erskin (13) voices the growing conviction when he states that "whether gastric ulcer frequently becomes cancerous is no longer in dispute, and it is now fairly well established that the incidence of gastric carcinoma is not increased among ulcer patients. It is also a fact that cancer of the duodenum is extremely rare, although duodenal ulcer is more common than gastric ulcer." The conception of the malignant degeneration of ulcer has been fostered by the idea of chronic irritation. Upon the current conceptions of the peptic genesis of ulcer there would seem to be more reason to speak of cancer-ulcer than of ulcer-cancer, since there are essentially two distinct types of gastric ulcer, the benign and the malignant ulcer; in the latter a primary cancer may provide the point of localized digestive action in an otherwise quiescent ulcer *milieu*. Their coincidence is fortuitous. It is possible, if not probable, that the abnormlly prolonged digestive action in an ulcer *milieu* could even eradicate a primary cancer and thereby effect the change of a cancer-ulcer into a benign ulcer. This is at least as probable as is Bloomfield's (10) suggestion of "two types of cancer of the stomach of fundamentally different origins" . . . . . "to be differentiated with considerable certainty by the presence or absence of acid in the gastric secretion." This conception seems to attempt to harmonize the discrepancies which arise when gastritis, in its acid and anacid types, is considered the cause of cancer.

The association of cancer and achlorhydria has long lost its diagnostic significance since the diagnosis of cancer has become more promptly and readily made and cancer is now found in an acid secreting stomach in at least one-third of the instances. Our clinical desire to observe a patient with achlorhydria for its several common associations is in reality based upon the persisting uncertainties of diagnosis rather than upon a definite likelihood of a known sequence in pathology. The development of parallel curves of incidence in the relation of cancer and achlorhydria to age is without direct significance as to their etiological relationship, and evidence, as with other diseases, only the common increase in incidence which characterizes the degenerative period of life.

The inference of gastritis from the mere findings of an achlorhydria or of an achylia is wholly untenable. It is asserted that with achylia of long duration there are always signs of gastritis, but admitting this fact, there has been no continued clinical observation of the inception and duration of either condition which would indicate the essential etiological relationship of gastritis. Bloomfield and Polland (17) find "that a lesion, which the pathologist classifies as 'gastritis' varies in extent and severity, it may be patchy or diffuse, and in any case it is not a specific lesion of anacidity, since similar changes have been found over and over again in stomachs from patients who, during life, had normal gastric secretions." Neither has the association been proven as constant. The association of chronic inflammatory changes in the stomach and of degeneration of the epithelia and glandular structure with pernicious anemia has been a persistent finding since their recognition merely as atrophy even prior to the discovery and demonstration of achlorhydria by gastric intubation. In the long period since the introduction of gastric analysis, the question of antecedence of these associated abnormalities has not been answered, and their causal or secondary relationship remains in doubt. Jones, Benedict and Hampton (18) report observations upon the gastric mucosa in pernicious anemia cases and find that, following specific therapy, evidence of atrophy and hypertrophy of the stomach, both tend to disappear. They think the correction of the atrophy results from the successful treatment of a deficiency state and the correction of the hypertrophy represents a subsidence of a chronic gastritis. This would indicate the mucosal inflammation to be secondary or at least a co-ordinate change. It is interesting to note that in ulcer cases of long duration in which gastritis may be presumed, according to surgical findings, to have co-existed, there is no development of achlorhydria. This failure is in a way unfortunate as it would provide conditions for the healing of the localized ulcer lesion and thus make the disease of peptic ulcer self-limited.

There is little opportunity in these cases of functional failure to secure histological information concurrent with the other clinical studies. Gastroscopy may be expected to help in this deficiency; however, in its practice gastroscopy will be an accessory rather than a primary or routine method of investigation. Simpson (19) says: "it is clear that the incidence of achlorhydria increases with age whether organic disease outside the stomach is present or not. In other words, there is no evidence that disease other than that of the gastric mucosa brings about achlorhydria. If evidence of organic disease is lacking, the assumption that the increasingly frequent anacidity is due to gastritis is the only logical one." To assume that secretory failure implies gastritis is to deny that secretory failure may arise from other phenomena. The question of a failure in the normal nervous and humoral stimuli has received no attention. Analogy must also imply that the functional failure of other secretory structures both internal and external must arise from inflammation. Other evidence of gastritis is usually lacking in instances of achlorhydria. That it may occur from biological protoplasmic failure is shown by the few cases in which an achlorhydria and the absence of the 'intrinsic' factor of the anti-anemia principle have been dis-associated, (20); also by the experimental findings of Babkin (21) "that in vitamin deficiency (general) there is a great impairment of the secretory response of the (dog) stomach to sham feeding, subcutaneous injection of histamine and introduction into the small intestine of food and five per cent alcohol. By the administration of yeast, normal relations were restored in a few days." This certainly demonstrates that a biological inadequacy may cause a

secretory failure. Christy (22) calls attention to the association of achlorhydria with other manifestations of nutritional deficiency and non-inflammatory primary changes in other than gastric tissues. The conception of a biological inadequacy is further supported by the occurrence of achlorhydria as a sequel to chronic debilitating diseases,—tuberculosis, malaria, colitis, dysentery, diabetes, chronic pyogenic suppurations, and is associated with asthenia, migraine, urticaria, pellagra, scorbutus and exopthalmic goitre. However, the frequent use of the term 'gastritis' to denote these changes in the parenchyma due to malnutrition, effects of pyrexia and hypothetical toxins is at best confusing.

It is impossible to believe that the demonstration of achlorhydria necessarily implies in any or all these diseases the presence of gastritis and the increased frequency of achlorhydria during the physiological stress of pregnancy suggests in that instance a systemic rather than a local cause. The same doubt may exist, of the essential occurrence of gastritis for the failure of the hemapoietic (intrinsic) factor and of the neurotropic factor, if such exists, as for the achlorhydria, in spite of the few recorded cases in which it has been demonstrated three months to twenty years prior to the diagnosis of pernicious anemia.

Macklin (16) says: "that achylia of certain types, perhaps all, is inherited, mostly in direct line of descent, passing on from parent to child," and Connor (23) having examined a large number of blood relations of pernicious anemia patients, believes that although "the results do not prove an hereditary aspect of pernicious anemia, they strongly suggest a familial tendency in the development of one of its most important features"—achlorhydria.

Faber states that chronic achylia has an exogenous cause and is produced by external factors acting on the stomach, either by direct irritation of the mucous membrane or through the blood circulation by a toxic action on the gastric parenchyma, causing not a superficial catarrhal inflammation but an effect on the glandular parenchyma. This is plainly a hypothesis and not a statement of objective fact and even as a hypothesis indicates a bio-chemical effect rather than an inflammatory reaction. A distinction must be made between a primary inflammation and a primary cell dystrophy arising either from nutritional deficiencies or from protoplasmic poisons.

Bloomfield concludes from his studies that gastritis is not a specific lesion of anacidity and, that anacidity as a precursor of or the cause of certain diseases, is possible but not finally proved by valid statistics.

That this problem of the possible sequence of gastritis to cancer, to ulcer or to the loss of mucosal secretory function is susceptible to experimental demonstration analogous to clinical occurrence, is not conceivable. It is a weakness in logic, when a condition associated with several diseases, is considered to be etiological in each connection. Causal influences and agents usually may be expected to have certain definite and predictable effects. Nothing has yet been developed in our knowledge of gastritis, to indicate any such possibility.

Howe (24) in discussing the causal fallacy, says: "there is one point, however, which every science or art must have in common with metaphysics, and that is its dependence upon some fundamental concept or elementary working hypothesis. The imposing structure of the completed edifice sometimes hides from us the fact that there must be a foundation somewhere. It is rather shaking to our scientific certainty when we realize that the nature of that foundation is nothing more secure than a hypothesis."

"The danger of a hypothesis is that it may be taken as an axiomatic statement which is therefore assumed to require no proof. There is no difficulty in checking up the error of one hypothesis by inventing others as required to fill the gaps which the original hypothesis fails to explain. This is a very general scientific tendency and accounts for the large number of hypotheses which pass as scientific facts." "A hypothesis is never at its best when used as a part of our therapeutic armamentarium but it is an essential weapon of research."

I find it impossible to harmonize the discrepancies which are found to exist when the hypothesis of gastritis as the causal precursor of peptic ulcer, cancer, achlorhydria and its association of anemia and cord degeneration, is examined. Gastritis, however, does merit in itself the revived and increased attention which is being given it.

In reviewing this hypothesis, it appears that gastritis in the sense of primary mucosal inflammation, is more likely to be in most instances a sequel or complication of peptic ulcer. In those cases in which it may have been prodromal, additional factors must be found to account for the localization of the ulcer within or without the gastritis area, factors which would, and do, operate also in the absence of gastritis. Cancer of the stomach is not in any way dependent upon or promoted by a sub-stratum of gastritis, and there has yet to be shown that there may arise from gastritis any carcinogenic factor by which an acquired disease could promote an hereditary disease. Achlorhydria and its associated secretory failures with their remote influences are more likely to arise from primary biological failure of the gland cells than to be essentially secondary to primary mucosal inflammation.

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SECTION II—*Experimental Physiology*

Pancreatic Enzymes and Tissue Metabolism*†

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RECENT articles in this Journal have ascribed to the pancreas an extraordinarily important role in metabolism. W. Boldyreff (1) states that the non-secreting tissues of the body, such as muscle, liver, spleen, etc., are unable to produce enzymes of their own and must therefore depend upon the secretions of the pancreas and intestinal glands for their supply of lipase, amylase, protease and glycolytic enzymes. The external secretion of the pancreas, according to this author, is absorbed completely from the intestine into the blood, and thus becomes in reality its internal secretion. The enzymes are then fixed by the tissue cells throughout the body. Oelgoetz, Oelgoetz, and Wittekind (2) carry the hypothesis a long step farther and state that the blood vessels constitute the main digestive organ of the body. Food and enzymes are mixed in the intestine, and together absorbed by the blood where the major steps of digestion occur. In the case of proteins, gastric and intestinal digestion may carry them through the preliminary change to acid and alkali metaproteins, but these, along with the proteolytic enzymes are absorbed as such and are finally digested in the blood. "The blood therefore may be regarded as a more important final digestive organ than is the gastro-intestinal tract." The tissues are said to contain these same enzymes, derived from the intestinal tract, and at a concentration one hundred times that found in the blood.

The three papers cited above contain little data in substantiation of the assumptions made. Boldyreff offers no data, but cites his earlier work in proving rhythmic activity along the intestinal tract as evidence in favor of the hypothesis (3). The papers by Oelgoetz, Oelgoetz, and Wittekind describe a rough method for determining the iodine absorbing power of serum, and state that this is a test for amylase. They also state without evidence that the pancreatic enzymes are always present in the blood, and in fixed proportions, so that the determination of one of them is sufficient to determine the concentration of them all.

It is not our intention to attempt a critical analysis of the details of these papers, many of which are quite counter to data in the literature. In the following paragraphs, however, we will submit concrete evidence which bears directly upon the major premise of these papers—namely, that pancreatic enzymes are present in the tissues; that tissue cells are unable to produce their own enzymes, and must depend upon the pancreas for a continually renewed supply in order to carry on the syntheses and hydrolyses incident to metabolism. If trypsin can be found in significant amount in tissues other than the pancreas, it would appear to give strong support to the hypothesis of Boldyreff. If trypsin cannot be demonstrated, it would appear to leave the hypothesis without factual justification.

We have chosen trypsin because its properties are so unique and so well characterized that there is no danger of mistaking some other proteolytic enzyme for it if the experiments are adequately controlled. The same cannot be said perhaps for lipase and amylase of the pancreas. Similar enzymes are widely distributed, and while we believe there are differences between the lipase of the pancreas and that of the liver or kidney, they are not so convincing as the differences between trypsin and other proteases.

In an earlier publication we presented some data which at the time we felt was fairly good evidence that trypsin is not one of the proteases of liver or kidney (4). In the following experiments we have again sought this enzyme under even more carefully controlled conditions. The data appears to be unequivocal and so far as it goes should definitely set at rest the question of whether pancreatic enzymes are present normally in tissues other than the pancreas.

EXPERIMENTAL PART

Hog pancreas, spleen and liver were obtained within a few minutes of the death of the animal. They were re-

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frigerated at once, ground to a smooth brei, weighed out in 50 gm. portions, and made up to a final volume of 250 c.c. in each case. Toluol was added as a preservative, care being taken to keep the digests saturated with it by frequent shaking during the first twenty-four hours. Experience has shown that under these conditions no bacterial growth occurs, and the digests remain sterile indefinitely. The digests were maintained at 37° throughout the period of study. Acid and alkali were added as indicated in the tables, and the pH levels determined potentiometrically. As has been shown previously (5), the pH values of such digests change during the period of digestion, the shift being in the direction of neutrality. The value of the pH control therefore is chiefly to determine whether the environment is satisfactory for the activity of a given enzyme or not. Trypsin is most active at about pH 8, but is still quite active at 6. On the other hand, we have previously shown (4) that typical autolytic proteases are most active in the neighborhood of 4.

Evidence of digestion was obtained as follows: twenty-five c.c. samples of the digests were removed at the start, and from time to time thereafter, as shown in the tables, run into 50 c.c. 10 per cent trichloracetic acid and made up to 100 c.c. After some hours the precipitated proteins were filtered off and the filtrate assayed for soluble N by Kjeldahl, for amino acidity by Sörensen titration, for reactive tyrosine by a modification of the Folin colorimetric method (6). Soluble N is perhaps the best method we have for measuring the rate and extent of primary cleavage of the tissue proteins. The tyrosine reaction gives essentially the same picture, because the initial breaks in the protein molecule serve to unmask most of the tyrosine (5). The Sörensen titration gives the same information, and in addition gives evidence for the further cleavage of non-precipitable protein fragments after the initial solubilizing cleavages have been completed.

RESULTS

In the data collected below we are presenting, for the sake of brevity, only the figures obtained by Sörensen titration. The other data, however, is in complete harmony with it. The experiments recorded here have been repeated many times, and are typical.

From the data above we draw the following conclusions:

TABLE I

Self-Digestion of Hog Pancreas

No.	Digests	pH Initial	c.c. N/5 amino acid in 25 c.c. trichlor. filtrate			
			Days			
			0	1st	3rd	10th
1	Control	6.16	0.40	3.90	4.45	4.50
2	Control + 25 c.c. N/5 HCl	4.48	0.40	2.80	3.90	4.10
3	Control + 50 c.c. N/5 HCl	3.35	0.40	1.30	2.25	2.90
4	Control + 75 c.c. N/5 HCl	2.57	0.40	0.60	0.65	0.70
5	Control + 20 c.c. N/5 NaOH	7.14	0.40	4.35	4.30	4.35
6	Control + 30 c.c. N/5 NaOH	7.37	0.40	4.35	4.35	4.35
7	Control + 40 c.c. N/5 NaOH	7.62	0.40	4.35	4.35	4.40

TABLE II

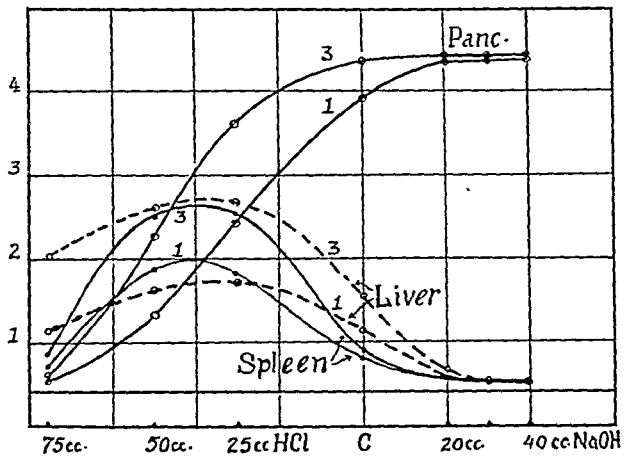
Hog Spleen

No.	Digests	pH Initial	c.c. N/5 amino acid in 25 c.c. trichlor. filtrate				
			Days				
			0	1st	3rd	5th	10th
1	Control	6.45	0.40	0.75	0.85	1.00	1.20
2	Control + 25 c.c. N/5 HCl	4.56	0.40	1.65	2.35	3.00	3.00
3	Control + 50 c.c. N/5 HCl	3.92	0.40	1.85	2.50	3.00	3.00
4	Control + 75 c.c. N/5 HCl	2.96	0.40	0.75	1.00	1.10	1.00
5	Control + 20 c.c. N/5 NaOH	8.56	0.40	0.55	0.55	0.65	0.65
6	Control + 30 c.c. N/5 NaOH	9.05	0.40	0.50	0.50	0.55	0.60
7	Control + 40 c.c. N/5 NaOH	9.33	0.40	0.45	0.45	0.55	0.50

TABLE III

Hog Liver

No.	Digests	pH Initial	c.c. N/5 amino acid in 25 c.c. trichlor. filtrate				
			Days				
			0	1st	3rd	5th	10th
1	Control	6.38	0.40	1.10	1.50	1.60	1.90
2	Control + 25 c.c. N/5 HCl	4.52	0.40	1.70	2.60	2.70	2.75
3	Control + 50 c.c. N/5 HCl	3.95	0.40	1.60	2.60	2.85	3.10
4	Control + 75 c.c. N/5 HCl	3.16	0.40	1.15	2.05	2.05	2.20
5	Control + 20 c.c. N/5 NaOH	7.00	0.40	0.65	0.70	0.75	0.90
6	Control + 30 c.c. N/5 NaOH	8.15	0.40	0.55	0.55	0.55	0.65
7	Control + 40 c.c. N/5 NaOH	8.70	0.40	0.50	0.55	0.55	0.60



Curve 1. Digestive patterns of pancreas, liver and spleen; 1st and 3rd day.

(1) Pancreatic tissue digests most rapidly when made alkaline. Tissue acidity developed post mortem, or by the addition of acid to the digests retards the process. The more acid added, the slower the proteolysis. In the brei to which 75 c.c. N/5 HCl was added, practically no digestion occurs in ten days. The digestive pattern of this tissue is overwhelmingly of the trypsin-erepsin type.

(2) Under identical conditions the spleen digests most rapidly in those breis to which 25 and 50 c.c. N/5 HCl had been added. There is some digestion even where 75 c.c. N/5 HCl was added, and a pH of 2.96 attained. There is barely detectable digestion in the presence of 20 c.c. N/5 NaOH, and none at greater alkalinities. The spleen therefore gives a digestion pattern fundamentally different from that of the pancreas, and specifically fails to show proteolysis where the pancreas digests at maximum rate.

(3) The liver under the same conditions behaves like the spleen. There is considerable digestion at the highest acidity, while more than 20 c.c. N/5 NaOH inhibits proteolysis completely.

If no digestion takes place at reactions optimum for trypsin, we must conclude that either there is no trypsin present, or that the tissue proteins are resistant to trypsin. The following experiments therefore were made to determine whether liver and spleen proteins, under the conditions described, digest in the presence of small amounts of trypsin.

A 10 per cent suspension of the pancreatic tissue in water was added to spleen and liver breis in the amounts shown in the tables. To each digest was added 30 c.c.. N/5 NaOH to inhibit autolysis and to give a reaction favorable for tryptic activity.

It is evident that 1 c.c. of the suspension, corresponding to 0.1 gm. of the pancreas tissue, added to 50 gms. liver or spleen is quite sufficient to produce obvious digestion of the tissue proteins within 3.5 hours. One-tenth of this amount would certainly be recognized in less than 24 hours. The organ proteins are readily digested, and a very minute trace of the enzyme will disclose itself under the conditions of these experiments. If trypsin is present at all in liver or spleen, it must be in amounts below the threshold of detectability by the method used, and we submit that an undetectable trace is of doubtful metabolic significance.

While liver and spleen show no evidence of trypsin, they both demonstrate an abundance of the tissue proteases associated with autolysis. Both digest somewhat between a pH of 2.5 and 3, where trypsin is quite in-

TABLE IV

Liver and Pancreas

No.	Digests	c.c. N/5 amino acid in 25 c.c. trichlor. filtrate					
		Hours				Days	
		0	3.5	5.5	10	1st	2nd
1	Control liver + 30 c.c. N/5 NaOH (pH 8.1 + Initial)	0.30	0.30	0.30	0.30	0.35	0.40
2	Control liver + 30 c.c. N/5 NaOH + 0.1 gm. pancreas	0.30	0.60	0.70	0.90	1.15	1.40
3	Control liver + 30 c.c. N/5 NaOH + 0.2 gm. pancreas	0.30	0.85	1.25	1.40	2.00	2.40
4	Control liver + 30 c.c. N/5 NaOH + 0.5 gm. pancreas	0.30	1.05	1.90	2.20	2.75	3.30
5	Control liver + 30 c.c. N/5 NaOH + 1.0 gm. pancreas	0.30	1.75	2.30	2.70	3.30	3.90

TABLE V

Spleen and Pancreas

No.	Digests	c.c. N/5 amino acid in 25 c.c. trichlor. filtrate					
		Hours				Days	
		0	3.5	5.5	10	1st	2nd
1	Control Spleen + 30 c.c. N/5 NaOH (pH 9.0 Initial)	0.75	0.75	0.70	0.80	0.80	0.90
2	Control Spleen + 30 c.c. N/5 NaOH + 0.1 gm. pancreas	0.75	0.90	1.00	1.15	1.80	1.90
3	Control Spleen + 30 c.c. N/5 NaOH + 0.2 gm. pancreas	0.75	1.00	1.20	1.40	2.30	2.40
4	Control Spleen + 30 c.c. N/5 NaOH + 0.5 gm. pancreas	0.75	1.30	1.50	2.00	2.75	2.75
5	Control Spleen + 30 c.c. N/5 NaOH + 1.0 gm. pancreas	0.75	1.50	1.90	2.20	3.10	3.10

active, and where pancreatic juice is also without proteolytic activity. This is sufficient evidence that Boldyreff's statement, "There are no endogenous ferments prepared by the cells themselves for the needs of general intra-cellular digestion (splitting and reconstruction of carbohydrates, fats, and proteins)," is incorrect. Liver and spleen contain an abundance of an enzyme group not present in pancreatic juice.

DISCUSSION

The evidence presented above we believe suffices to raise fundamental doubts as to the validity of Boldyreff's whole hypothesis. The literature is full of competent data too numerous to mention in detail here, which must be ignored if one accepts his theory. The extensive literature of autolysis negates it (7); Kathepsin is a well characterized protease not demonstrated in pancreatic juice (8); animals have been kept alive for long periods without their pancreatic gland, and without pancreatic feeding, provided insulin and lecithin or choline is supplied (9). One might well inquire what the evidence is upon which so far reaching a theory has been based, which at the same time appears so definitely counter to generally accepted experimental data.

In his previously published papers, in which the theory is first advanced, Boldyreff has been concerned with the phenomenon of rhythmicity along the alimentary tract. He demonstrates with a wealth of recorded observations a periodic activity which includes peristaltic waves and secretion of intestinal and pancreatic juice. The secretions are enzymatically active, although there is no food material in the tract. The juices secreted in the upper segments of the small intestine are practically all absorbed before the colon is reached, and the enzymes disappear. At least there appears to be no concentration of enzymes.

Rhythmic activity together with actual disappearance of juices and enzymes in the fasting intestine has led Boldyreff, therefore, to conclude absorption, distribution to the tissues, and the utilization of these enzymes in tissue metabolism. So far as we have been able to discover, that Author has not presented any further experimental evidence for the hypothesis. Instead, he has accepted reports from the older literature before there was adequate characterization of some of the enzymes, and before control and designation of the H ion level was possible. The fact of rhythmicity, and of disappearance of digestive factors from the non-digesting intestine does not in any way prove that these enzymes are lodged in the liver or spleen. Nor can we accept today, as authentic evidence of trypsin, such observations as that of Theobald Smith, made in 1894 (10), that sterile pieces of liver, spleen, and kidney liquefy gelatin. Yet this is the sort of evidence which Boldyreff cites to prove that these tissues do contain this enzyme. As a matter of fact, Smith himself did not draw this conclusion. He correctly regarded the liquefaction of gelatin by sterile tissue as enzymic digestion of the gelatin, and describes the action as "trypsin-like." We recognize today that Smith was dealing with the autolytic mechanism, in this interesting early observation. It is now well known that liver, spleen, or kidney made alkaline enough to completely inhibit autolysis will still digest peptone, gelatin, and casein. But the protease of the tissue which effects this cleavage will not attack the native tissue proteins. It is therefore not trypsin.

We are not questioning the fact that traces of the digestive enzymes are absorbed from the intestine from time to time, just as traces of undigested proteins are. Pepsin and trypsin have frequently been reported in the urine, and these reports are cited by Boldyreff as confirming his theory of metabolism. Actually, of course, trypsin in the urine is no evidence at all of trypsin in the liver. Nor is food allergy, which obviously depends on the absorption of specific food antigens from the intestine, any evidence that protein digestion is largely accomplished by pancreatic enzymes in the blood stream, as maintained by Oelgoetz.

SUMMARY

1. Under optimum conditions for tryptic activity, spleen and liver of the hog show no proteolysis.

2. Very small traces of trypsin added to these tissues under the same conditions give unequivocal evidence of proteolytic activity.

3. We have been unable therefore to find any evidence in support of the theory that trypsin is absorbed as such from the intestinal tract, to be distributed to and fixed by the tissues for their metabolic use.

4. Spleen and liver cells contain proteolytic enzymes not found in pancreatic juice and therefore not supplied them by absorption of that juice. It is logical to assume that they are produced by the tissue cells themselves, until definitely proven otherwise.

5. Any system of physiology, pathology, and therapy, based upon the assumption that pancreatic enzymes are regularly present in tissues such as liver and spleen, should be accepted with caution until some competent evidence is forthcoming to substantiate it.

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The Influence of Bact. Coli and Its Products on the Motility of Strips of Excised Intestine*

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THE microorganisms which make up the so-called normal intestinal flora have quite generally been regarded as non-pathogenic so long as they confine their *habitat* to the intestine. Some have been found capable of setting up disease processes when they invade different parts of the body, as for instance, in *Bact. coli* cystitis, and *B. welchii* gangrene. However, it does not appear impossible that the bacteria normally present in the large intestine may at times account for organic and so-called functional diseases of the intestine itself. Brown (1925) believes that *Bact. coli* may play an etiological *rôle* in idiopathic ulcerative colitis. The bacteriological literature contains many references to the possible etiological significance of various members of the intestinal groups of bacteria in various pathological processes. We shall not attempt to review the entire literature here, but will cite several of the most recent publications which have appeared and which concern the organism upon which the main emphasis is placed in this paper.

Deak (1933) and Hassman and Herzman (1934) have shown that *Bact. coli* may be of etiologic significance in the enteric diseases of childhood. They believe that some strains of this organism are atypical, and have referred to them as "paracoli," because they do not ferment lactose. Some American investigators also have described paracoli strains, and have attributed to them an etiologic *rôle* in the summer diarrheas of children. Catel and Pollaske (1933), Silberstein and Singer (1924) and Rosenbaum and Chassel (1933) all worked with living and dead cultures of *Bact. coli*, and showed by various methods that this organism may play some part in the causation of intestinal disturbances. Adam (1927) and Goldschmidt (1933) demonstrated that *Bact. coli* can be toxic, and that when cultures are fed by mouth to animals they can set up an intestinal disturbance.

Hahsman and Scharfetter (1935) did considerable work with *Bact. coli* and studied its effect on the excised intestine of rabbits. They believe that filtrates of normal strains of *Baci. coli* do not affect the musculature of rabbits' intestine. Strains of *Bact. paracoli* obtained from children suffering from an intestinal disturbance always gave a definite response, usually increased peristalsis and tonus. Stronger concentrations of the filtrate paralyzed the peristalsis and tone. When the filtrates were allowed to act on the small intestine for a short time it was found that the reaction was reversible, but when allowed to act for a long time the reaction was irreversible.

Thus it can be seen, at least from the more recent literature, that the question of possible etiological relationships of the so-called normal intestinal bacteria is one of great importance and should be studied further. It is our purpose in this paper to present some findings regarding the action of a "normal" strain of *Bact. coli*, on excised strips of intestine.

EXPERIMENTAL

A strain of *Baci. coli* isolated from a normal human adult was used in all of the work reported here. Cultural and biochemical studies showed the organism to be of the *communior* type. The organism was grown in 2% Difco Bacto peptone water for twenty days; cultures so prepared constituted the material with which all of the tests reported here were carried out; this material was always distinctly alkaline. Studies were made with the whole culture, with the centrifuged supernatant, and with filtrates prepared from the culture, to determine their action on strips of excised intestine.

The cat was used as the experimental animal, since it could be procured easily at any time, involved little expense, and proved to be a fit subject for this type of experimentation.

The animals were sacrificed by stunning, and the strips of intestine used in the experiments were immediately removed and immersed in Ringer-Locke solution. They were stored (never more than two days) at refrigerator temperature before use. The strips of muscle were immersed in a bath of Ringer-Locke solution which was kept at 37° C and aerated by a stream of oxygen. The hooks and levers commonly used to obtain records of muscle contractions were attached to the strips and the movements recorded on a kymographic tracing moving at a standard rate of speed The muscle strips were held in the bath for at least thirty minutes in order to allow them to assume their normal rhythm. Definite but varying amounts of whole culture, centrifugate or filtrate, were then added to known volumes of the Ringer-Locke solution in which the strips were suspended. All of the test materials were heated to 37° C before they were placed in the bath. An uninoculated peptone mixture of the same composition as the culture, adjusted to the same pH and used in the same concentration, was always employed as a control.

EFFECT OF BACT. COLI CULTURES ON THE MOTILITY OF VARIOUS PARTS OF THE INTESTINE

Different parts of the intestine were subjected to the action of the *Bact. coli* cultures in an attempt to determine whether or not they reacted differently in manner or degree.

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Effect on Duodenum and Jejunum. It was found very soon in the investigation that the optimum amount of whole culture which should be used to elicit a maximum reaction was 10 per cent of the total volume of the bath in which the intestine was immersed.

The *Bact. coli* cultures, when applied to strips of duodenum and jejunum brought about a paralysis of the intestinal musculature. There was a definite inhibition of the contractions and an almost complete loss of tonus. This reaction took place within 30 seconds to one minute after the beginning of exposure.

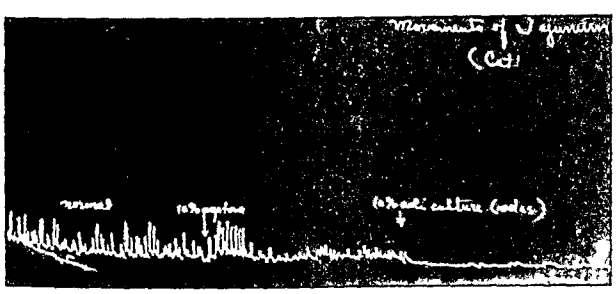


Graph 1. Effect of Bact. coli culture on Duodenum.

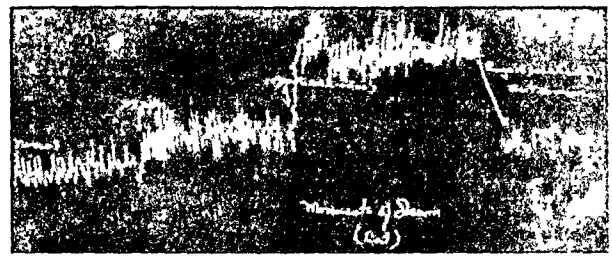
Uninoculated peptone water of the same composition as the medium in which the coli organisms were grown showed no effect when put into the bath containing strips of duodenum or jejunum, in the same concentration as the bacterial culture. (Graphs 1 and 2).

Effect on Ileum and Colon. The same cultures of *Bact. coli* (grown for twenty days in 2% peptone water medium), when added to a bath in which strips of ileum were suspended, gave a reaction which was directly opposite to the response elicited from the duodenum and jejunum. Within thirty seconds to one minute after the addition of the whole culture to the Ringer-Locke solution the strip of ileum responded with a very definite increase in tone and a speeding up of its contraction rate. A 2% solution of uninoculated peptone water gave no reaction except a slight rise in tone which was shown on numerous occasions to be of a very transitory nature.

The *Bact. coli* culture, when allowed to act on strips of colon immersed in a Ringer-Locke solution, elicited the same type of response as from the ileum; but the increase in tone was much less than that of the ileum, and was only moderately higher than that brought about by the addition of sterile peptone solution. There was, however, quite a marked increase in the rate of contraction of the muscle strip. (Graphs 3 and 4). It was observed throughout this study that the colon reacted much more slowly to all of the applied agents, and that it required a relatively long time after first being put into the bath to become stabilized and give a normal contraction curve. Perhaps a much more



Graph 2. Effect of Bact. coli culture on Jejunum.



Graph 3. Effect of Bact. coli culture on Ileum. Reversibility of the Reaction.

definite response would have been elicited if we had used greater concentrations of culture; but this was deemed inadvisable because of the possibility of increasing the salt concentration to the point where it might induce a salt effect. While the results obtained with the strips of colon are very suggestive, no definite conclusions should be drawn from them.

Effect of Centrifuge Supernatant and Filtrate of Whole Culture. Attempts were made to demonstrate the presence of the substance (or substances) which was the active agent in the whole cultures of *Bact. coli*, in the centrifuge supernatant and filtrate of the culture. The cultures were centrifuged at high speed for about twenty minutes, and the supernatant fluid carefully pipetted off. This was then added to the Ringer-Locke solution in the bath in the same concentration as was the whole culture. In every instance the action of the supernatant fluid was essentially the same as that of the whole culture. It varied with the portion of the intestine exposed to it: that is, the ileum and colon were stimulated and the duodenum and jejunum depressed. The intensity of the reaction was in the same general range as that obtained with the whole culture, taking into account the normal variation in the reaction ability of different pieces of intestine from different animals.

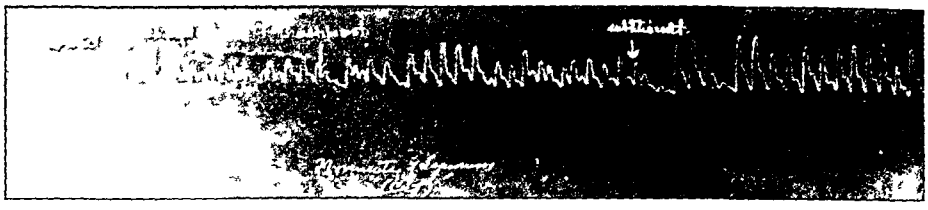
Chamberland (L3) filtrate of the whole culture was applied in the same way as the whole culture and supernatant. The active substance was found to be present in the filtrate also. (See Graph 8). The response of the strips of intestine was in general weaker, however, to the filtrate than it was to the whole culture or to the supernatant. The weaker action may be accounted for, at least in part, by the removal of some of the physiologically active substance from solution by the filter.



Graph 4. Effect of Bact. coli culture on colon.

Influence of Length of Incubation of Cultures on Amount of Active Material Produced in Them. An attempt was made to determine how soon the active substance is produced in sufficient concentration to call forth the typical maximum response. For this purpose a 2% peptone medium was inoculated with *Bact. coli*

and incubated at 37° C. Portions were withdrawn at various intervals and their action on strips of intestine determined. Samples taken after two days' incubation were found to exert the opposite action on strips of duodenum from that obtained with twenty day old cultures; that is, two day old cultures caused a slight increase in tone and contraction rate. The same was true for portions of the culture taken out at the end of five days' incubation. The findings were essentially the same with the whole culture, the centrifuge supernatant and the filtrate. (See Graph 5 and 6). By the end of ten days' incubation the substance (or substances) which caused depression of the duodenum and jejunum, and excitation of the ileum and colon, was readily demonstrable, although the reactions elicited with this material were not in every instance of as great magnitude as those obtained with material from twenty-one day old cultures. (See Graphs 2 and 3).



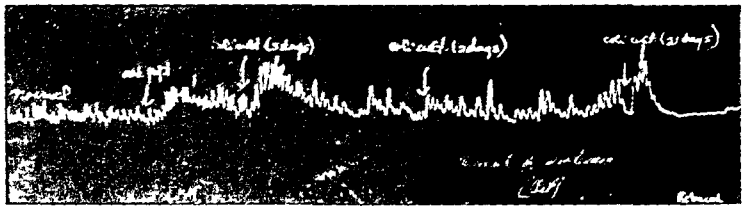
Graph 5. Influence of Length of Incubation of Cultures on Amount of Active Material Produced in them.

There are two possible explanations for the differences in the action of the young and older cultures. One is that the two substances are different in nature and that the first is destroyed during continued incubation at 37° C., possibly by the constantly increasing alkali that is formed in the culture. The other is that the two substances are one and the same in all instances, but that the reaction depends on the concentration of the active agent in the bacterial culture; in the two and five day old cultures the substance may be present in such small amounts as to bring about an excitatory response, whereas in the twenty-one day old culture its concentration is sufficient to exert a depressant action. This fact holds true for many of the exciting and depressing agents known to the pharmacologist; for example, alcohol in very small concentrations acts as a stimulant, while in greater amounts it exerts a marked depressant action.

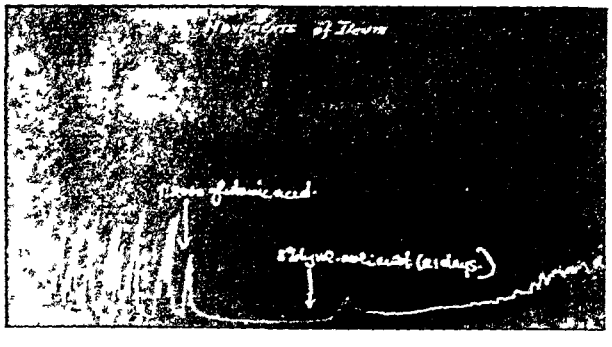
ABILITY OF THE INTESTINE TO RESUME NORMAL CONTRACTION AFTER TREATMENT

Experiments were conducted to determine whether the strips of intestine were capable of resuming normal contractions after they had been acted upon by the substances present in the coli cultures.

Strips of intestine were suspended in the Ringer-Locke solution and subjected to the action of *Bact coli* culture, supernatant and filtrate for varying periods of time. The bath was then emptied, new warm Ringer-Locke solution placed in it and the same strips suspended in the solution. It was found that strips of intestine from different parts of the tract could be subjected to the action of *Bact. coli* for periods ranging up to one-half hour without permanent damage to them. There was no apparent difference between the effects produced by the whole culture, the filtrate and the supernatant. (Graph 3).

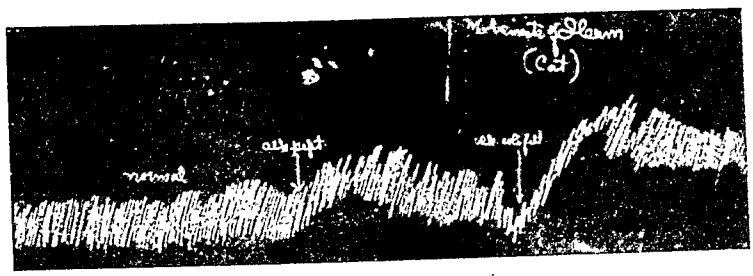


Graph 6. Influence of Length of Incubation of Cultures on Amount of Active Material Produced in them.

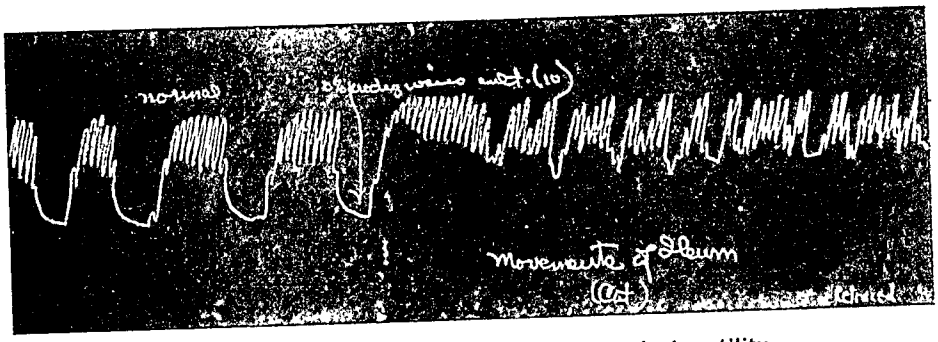


Graph 7. Specificity of the Reaction.

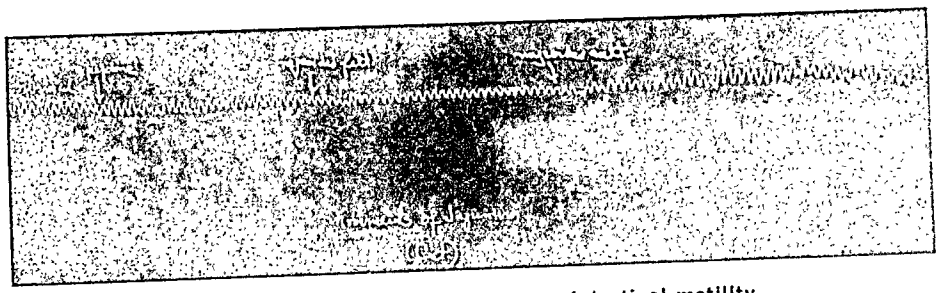
Specificity of the Reaction. In order to prove that the reaction to the products formed by *Bact. coli* was specific for this organism the following experiment was performed. Strips of intestine were subjected to the action of 1:1,000 glutamic acid, which had been shown before to paralyze intestinal movements, until all motility had disappeared and there was a loss in tone. When the reaction to the acid had been allowed to proceed for some time, coli culture was added. In every instance the culture tended to exert a neutralizing influence on the action of the glutamic acid. The experiments were conducted only with strips of ileum and jejunum, since all portions of the intestine were found to be paralyzed by the glutamic acid. The



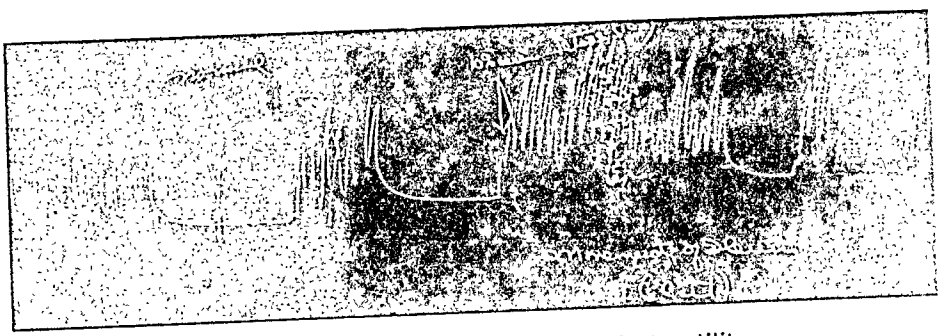
Graph 8. Effect of Filtrate of whole culture.



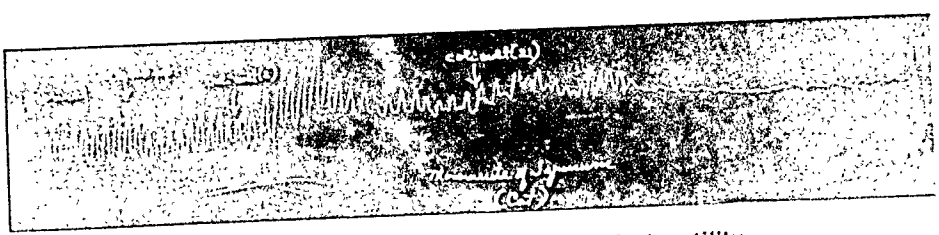
Graph 9. Effect of S. marcescens on Intestinal motility.



Graph 10. Effect of B. mycoides on Intestinal motility.



Graph 11. Effect of B. cereus on Intestinal motility.



Graph 12. Effect of B. subtilis on Intestinal motility.

strips of ileum were made to undergo an increase in tone and a marked speeding up in their contraction rate by the addition of the *Bact. coli* after they had been acted upon by 1:1,000 glutamic acid. This experiment was repeated several times, with similar results; that is, the muscle tissue could be paralyzed by glutamic acid, revived by coli culture, paralyzed again with glutamic acid, and revived again by the coli culture. One phase of this reaction is recorded in Graph 7.

Effect of Cultures of Other Bacteria. In order to determine whether the property of eliciting the reactions described above is common to bacteria generally, or one that is specific for the colon bacillus, experiments were conducted with other bacteria, namely *S. marcescens* (prodigiosus) *B. subtilis, B. cereus* and *B. mycoides.* All were grown in 2 per cent peptone water at room temperature for from ten to twenty days, and added to the Ringer-Locke solution in the same proportion as were the *Bact. coli* cultures. No definite effects on the movements of the intestinal strips could be obtained with any of these organisms. Neither the whole cultures, their filtrates nor the centrifuge supernatants caused any definite response in the intestinal muscle. *S. marcescens* at times caused the intestinal muscle of the ileum and colon to undergo a slight increase in tone. This response, was, however, of a much lesser magnitude than that obtained with *Bact. coli* and could not be obtained with every strip of intestine used. Portions of the culture taken out at different periods of incubation showed that no reactive substance was present at any time. The results are shown in Graphs 9 to 12.

DISCUSSION

The problem of determining physiological responses to bacterial cultures is of necessity a very complicated one, because of the highly complex nature of the cultures. Attempts to pin down the reactive influence to one substance would seem rather futile, since the responsible material in the present study may be a purely metabolic product, an exotoxin or some endotoxic substance released from the cell by autolysis in a highly alkaline medium. That *Bact. coli* may produce amines and diamines, *e.g.* histamine, as was shown by Hanke and Koessler (1922), is accepted by bacteriologists generally. A definite specific exotoxin or endotoxin of *Bact. coli* has apparently not been demonstrated up to the present time. In this work we make no attempt to define the reactive substances, but merely wish to impress the reader with the fact that there is present in cultures of *Bact. coli* some substance (or substances) which exerts a definite effect on the motility of excised strips of intestine. This finding is in harmony with the observations of some of the investigators mentioned in the introduction.

Another point in these experiments which seems to us to be worthy of notice is the difference in the reactions elicited from the various portions of the intestine. The duodenum and jejunum gave responses directly opposite to those of the ileum and colon. Different chemical substances, histamine, adrenalin and various amino acids employed by Weinstein and Cowgill (unpublished) elicited the *same* response from *different* parts of the intestine. Three possible explanations for this difference in reaction suggest themselves to us. (1) The difference in reaction may be caused by a difference in the nervous elements in the walls of different parts of the intestine. (2) The *Bact. coli* culture may contain two different substances, one acting on the duodenum and jejunum to depress them, but having no effect on the ileum and colon, and the other acting on the ileum and colon in the stimulatory manner, but having no influence on the motility of the duodenum and jejunum. (3) The difference in effect may be due to a sensitizing effect brought about in the following manner: the duodenum and jejunum rarely harbor *Bact. coli,* while the ileum (especially the portion near the ileo-cecal valve) and the colon are in life in constant contact with *Bact. coli* and its products; the continued contact with this organism may cause the mucosa of the ileum and colon to become sensitized to products of *Bact. coli,* so that when these products are suddenly brought into contact with these tissues in high concentration a response quite different from that of non-sensitized tissue is brought about.

SUMMARY AND CONCLUSIONS

A substance (or substances) produced by *Bact. coli* in peptone water cultures which exerts a definite influence on the motility of excised strips of intestine has been demonstrated. This substance depresses the motility of the duodenum and jejunum and stimulates that of the ileum and colon. It is detected readily in cultures after ten to fourteen days' incubation.

The reactive material is present in the centrifuge supernatant and in filtrates of cultures of *Bact. coli.*

The reaction brought about by the culture material is reversible.

The reaction may be regarded as specific, since other bacteria, *S. marcescens, B. subtilis, B. cereus, and B. mycoides,* all of which are of non-intestinal origin, apparently do not produce substances which exert any definite action on the motility of the intestine.

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Observations on Ulcerations Adjacent to Experimental Gastric Pouches in Dogs*†

By

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NEW YORK, NEW YORK

WHILE studying the chemical phase of gastric secretion in a dog prepared with an abdominal wall "nerveless" gastric pouch†† a large area of ulceration was noted in the abdominal wall adjacent to the pouch orifice. The ulceration was 8 cms. long, 6 cms. wide and 3 cms. deep. During the oestrus, which occurred a short time later, this large ulcerated area healed completely. A similar healing of such ulcerations during oestrus had been noted on two other occasions in this dog and three times in another "nerveless" pouch dog. In this connection it is interesting to recall that the late Dr. Eugene Klein had already noticed and reported (1) that in four dogs there was an increase during lactation in the secretory activity and skin erosions about the "nerveless" chemical pouches. It was therefore thought important to make further observations and experiments on the relationship of the sexual cycle, the female sex hormones, and, certain ductless glands to such ulcerations appearing about gastric pouches.

In the female dog with the "nerveless" pouch, (Dog 1, "Alma"), following the healing of the abdominal wall ulceration during oestrus, renewed ulceration appeared in the latter part of the ensuing pregnancy. This area measured 4 by 3 cms.

Following the line of reasoning that the ovarian follicular hormone is chiefly responsible for the oestrus and was in some way associated with the healing during oestrus, and, a definite area of ulceration being established, during the next ten days, the follicular hormone "Theelin"**, 250 rat units b.i.d. was given subcutaneously. At the end of that period the ulceration was practically entirely healed. Five test meals of meat, 150 gms., and water, 200 ccs., averaged 4.9 ccs. secretion in 4 hours, 18 units free hydrochloric acid with a peptic activity of 2 mms. digestion in a Mett's tube.

The dog was then untreated during the next 3 weeks. A large area of ulceration measuring 8 by 5.5 cms. developed. A test meal during that period revealed 6.5 ccs. secretion, 30 free acid, and 2.5 mms. Mett's tube digestion.

The dog then gave birth to 9 puppies. During the lactation of 3 weeks the area of ulceration enlarged to 8.5 by 8 cms. A test meal during that period revealed only 0.85 ccs. secretion, 10 free acid and 2 mms. peptic activity.

Following this period of lactation, the ulceration healed completely in 4 weeks. Three test meals during that period averaged 3 ccs. secretion, 20 free acid, and 2 mms. peptic activity. This healed state persisted for the next two months. Test meals during that period averaged 3.1 ccs. secretion, 36 free acid, and 1 mm. Mett's tube digestion.

Again, following the line of reasoning that the anterior pituitary secretion is increased and "Theelin" absent during lactation, and, that the lactation period was associated with increased ulceration, the "anterior pituitary-like" hormone, "Antuitrin-S," 2 ccs. intramuscularly q.d., was administered for 10 days. After 4 days, an area of ulceration measuring 6 by 4.5 cms. appeared about the pouch. A test meal during that time revealed 5 ccs. secretion, 20 free acid and 2 mms. peptic activity.

The dog then went into the oestrus and in that period there was a complete healing again. A test meal showed 0.8 ccs. secretion, with 0.0 free acid and 0.0 pepsin. During the next 4 months there was no ulceration. Pregnancy did not occur after this oestrus.

The second dog studied was a male dog with a typical Pavlov pouch, (Dog 2, "Pedlo") viz. a fundus pouch connected with the main stomach by a submucosal bridge thereby retaining the nerve and blood supply of the main stomach and thus mirroring its activities, including the vagus and chemical phases of gastric secretion.

Two weeks after the institution of this pouch, a large area of ulceration appeared measuring 5.5 by 3 cms. which persisted 10 weeks. Test meals during that period averaged 21.5 ccs., 80 free acid, and digested 4 mms. of a Mett's tube.

"Theelin," 250 rat units b.i.d. subcutaneously, was then administered for 3 weeks. The lesion definitely diminished in size, and, at the end of 3 weeks, the lesion was completely healed. Test meals during these 3 weeks averaged 10 ccs. secretion, 80 free acid, and digested 3 mms. in a Mett's tube. The healing persisted throughout the next 2 weeks. There was then a minimal secretion of 0.2 ccs., 60 free acid, and 1 mm. Mett's tube digestion.

The next experiment, in view of the healed state, was to administer "Antuitrin-S," 2 ccs. q.d. intramuscularly for 2 weeks. Ulceration commenced to appear about the pouch orifice in 4 days and at the end of 2 weeks had reached the large size of 5.5 by 3 cms. There seemed to be a constant oozing of free hydrochloric acid from the pouch mucosa. There was no change in the area of ulceration for 2 weeks.

Again, "Theelin," 250 rat units b.i.d. was administered subcutaneously for 3 weeks. The ulceration gradually disappeared within these 3 weeks. Test meals during this period revealed 3.5 ccs. secretion, 100 free acid and a digestion of 2.5 mms. in a Mett tube.

No further ulceration was noted in the next 10 weeks. Test meals during this period averaged 11 ccs., 120 free acid, and a peptic digestion of 2.5 mms.

COMMENT

In the female dog with the "nerveless" pouch, oestrus apparently in some way was associated with the healing of the ulcerations about the pouch. Renewed ulceration appeared late in pregnancy and at-

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†From the Pathology Laboratories, Mt. Sinai Hospital.

††This is a gastric fundus pouch invented by the late Dr. Eugene Klein in which the muscularis with Auerbach's plexus is stripped away and the mucous membrane pouch then implanted subcutaneously in the abdominal wall with a severance of the intra-abdominal blood and nerve supplies. This is the nearest approach to a completely nerveless pouch inasmuch as only Meissner's plexus is retained. The function of this plexus is unknown. Such a pouch secretes only in response to a chemical stimulus since the vagus phase has been completely abolished by the operative procedure.

(1) Klein, E.: *Arch. Surg.* 26:235 (Feb.) 1933.

**The "Theelin" and "Antuitrin-S" used in these experiments were obtained through the courtesy of the Research Dept. of Parke-Davis & Co.

tained its miximum during lactation. In the intervals between lactation and oestrus, in this dog at least, the ulceration may or may not appear. There does not seem to be a definite relationship between the secretory activity of the pouch and the amount of ulceration.

Experimentally, in this female dog, the ovarian follicular hormone ("Theelin") apparently promoted healing, or, at least, was in some manner associated with it. "Antuitrin-S" (the "anterior pituitary-like" hormone), on the other hand, seems to be associated with the production of ulceration. Here again the secretory studies did not demonstrate any definite relationship.

Considering the male dog with the Pawlow pouch, "Theelin" again was demonstrated to have a possible relationship to the healing and "Antuitrin-S" to increase ulceration in the abdominal wall contiguous to the pouch orifice. Here the large area of ulceration which appeared spontaneously before treatment was associated with a large amount of secretion from the pouch. Following "Theelin" administration, the quantity of secretion diminished markedly. However, an increase in secretion after "Antuitrin-S" was not noted.

The purpose of presenting these observations and experiments on the two dogs is to suggest the desirability of studying this problem systematically on a large scale. Furthermore, the possible relationship of such abdominal wall ulcerations about pouch orifices to internal ulcer of the mucous membranes of the stomach and duodenum should be considered. Of interest is the overwhelming predominance, in our experience, of human ulcer in the male sex.

DISCUSSION

DR. BORIS P. BABKIN (Montreal, Que.): The observations made by Dr. Winklestein on ulceration of tissue around the orifice of a gastric pouch are very interesting. The experiments on the relationship of the sexual cycle and some female sex hormones to such ulcerations are very suggestive, but the problem is too complicated to permit of drawing any definite conclusions.

Dr. Winklestein is very modest in his conclusions, presenting his observations and experiments with the chief aim of stimulating further work in this field; therefore, I should like to make only a few remarks and communicate to you the impression which I obtained in listening to this paper.

The figures of the volume of gastric secretion and its digestive power reported in Dr. Winklestein's work vary greatly and do not seem to stay always in a direct relation to the sexual cycle or to the administration of "Theelin" or "Antuitrin-S"; therefore, the formation of an ulcer around the orifice of the pouch seems to depend not on the amount of juice secreted or its digestive power during various periods.

It seems that the resistance to the peptic digestion of the skin, of the subcutaneous tissue, and muscles, is lowered during lactation on administration of "Antuitrin-S." It is true that during the lactation there was noted an increased secretory activity of the pouch. It must not be forgotten, however, that during the pregnancy, especially in its late stages, there is a continuous distension of the skin and its possible traumatization. With the onset of lactation and more profuse gastric secretion, this somewhat damaged tissue may undergo a much easier digestion than that of the normal tissue.

How complicated the problem of the inter-relations of endocrine glands and glands with external secretion is, may be shown by a few examples. According to Cushing, the undue secretion of the posterior pituitory lobe may be a factor in the causation of some gastro-intestinal disorders, including ulcers. One of Orbeli's pupils, on the other hand, showed that the administration of pituitrin to a dog with a gastric pouch produces a long, lasting depression of the gastric secretion, which could not be explained by vasoconstriction.

Another example: Dr. Winklestein noted during oestrus period or after administration of "Theelin," healing of the abdominal wall ulcers, and in some instances, although not always, a diminution of the gastric secretion. We have some occasional observations on female dogs with gastric pouches which definitely indicate that during oestrus the daily volume of the gastric secretion was almost doubled.

There is no need to try to resolve at the present time these and other controversial observations and facts. What is necessary now is a systematic study of the relations between the endocrine glands and the function of the gastro-intestinal tract. For certain reasons, and chiefly because the endocrinology itself is just emerging from a chaotic state, this was not done; therefore, Dr. Winklestein's work is valuable because it shows that such relationships exist and because it stimulates further investigations along these lines.

DR. A. C. IVY (Chicago, Ill.): Dr. Winklestein has made two very interesting and possible significant observations. One suggests that "Theelin" has an effect upon the healing processes; and the other is that "Theelin" depresses gastric secretion.

Now, in regard to the first indication, we know that "Theelin," or the sex hormones, are chemically related to growth promoting substances. For example: "Theelin" has a ring structure like the carcinogenic principle in coal tar products; so this is a bit of corollary evidence supporting the interpretation which he has suggested.

Now, in regard to the effect of "Theelin" on gastric secretion, the incidental observations that we have made in our laboratory on the effect of oestrus on gastric secretion are similar to those made by Dr. Babkin. In oestrus we generally observe the gastric secretory response to a meal to be augmented rather than depressed, and the same augmentation is generally true of gastric motility; however, that does not mean that the "Theelin" which we have available for use does not depress gastric secretion or even depress gastric motility, because "Theelin" may be different from the substance that is actually manufactured by the ovary in oestrus. Maybe the ovary is manufacturing something else. Maybe the situation is even more complex than that, as Dr. Babkin has suggested.

I am particularly interested in the possibility that "Theelin" may depress gastric secretion, and we at the present time have a number of dogs upon which we are making control secretory studies, with the intent later on of injecting some "Theelin" to see the effect of it on the gastric secretory response.

To my knowledge the effect of "Theelin" on gastric and intestinal motility has not been studied. It is a very important problem. It is also important to know the effect of "Theelin" and the various hormones associated with the female sex organs, on the gall bladder, because of the incidence of gall stones in pregnancy. There are reports in the literature which show that in some species, at least, in the latter part of pregnancy, the gall bladder does not evacuate normally; so that we have a very important field for investigation outlined, namely, the effect of the female sex hormones and associated hormones on the secretory and motor activity of various abdominal viscera.

DR. FRANKLIN HOLLANDER (New York City): Dr. Winklestein has asked me to mention to you several of my own observations on hypersecretion in dogs, provided with fundus pouches, during lactation.

The first of the series of observations was made quite accidentally. Subsequently it was possible to reproduce it under controlled conditions. Specifically the observation was this: We had occasion to prepare a fundus pouch of the Pavlov type on a dog in about the second week of pregnancy. In preparing this pouch we followed the usual practice in our laboratory of providing it with a sphincter at the mouth, just at the opening of the abdominal surface, by means of which sphincter it was possible to retain the secretion in the pouch for several hours at a time.

This modification of the usual technique was introduced for various experimental purposes and enabled us to measure the daily output of secretion with some accuracy. The animal was not used for experimentation for several weeks after the operation, although casual observations of the daily volume of secretion were made. During the four weeks between the preparation of the pouch and the dropping of the litter, the daily average output of gastric juice from this pouch was about 10 to 15 c.c. This was considered rather low for dogs that we had been preparing in our laboratory. The reason for the low value was not known at the time.

One morning when the animal man went to feed the dog in its kennel, a litter of pups was found. We were not sure, I may say, whether the animal was pregnant or not, at the time of the operation, because of various extenuating circumstances. The animal had ripped the dressing from off the abdomen, and although there had been absolutely no erosion around the pouch on the previous day, the erosion noticed on this morning was very extensive. It covered an area of more than the size of half a dollar, and was quite deep, and we were surprised to find that the pouch contained a very large amount of highly acid secretion.

We followed the acid output very carefully thereafter and observed that during three to four weeks of lactation the average rate of acid secretion was about 150 c.c. a day. On some days it rose as high as 200 or 250 c.c., and was continuous practically throughout the twenty-four-hour period. This, mind you, was in contrast with the situation previous to dropping of the pups, where we had an average daily output of no more than 15 c.c. The acidity both before and after this critical day was on the average the same. We were getting very pure gastric secretion, and the acidity was in the neighborhood of 150 to 160 clinical units, that is, 150 to 160 millimolar concentration.

This high rate of secretion continued during the three to four weeks of lactation. Thereafter the pups were weaned progressively and with this weaning we found a very marked falling off in secretion. By the end of the sixth week, the rate of secretion had fallen to about 30 c.c. per day on the average and dropped continuously thereafter. The animal was lost by an accident during the seventh week so it was not possible to continue the observations any further.

Subsequently we tried to reproduce this under more controlled conditions. Two pouch animals that had been prepared some time before, were mated. In both cases we got the hypersecretion, but in neither case was the increase in secretion nearly as high as that which had been observed in the first. Actually the average increase was no more than two or threefold, whereas in the first animal the average increase was tenfold or greater. Similar observations have been made by Dr. Eugene Klein and Dr. Ivy, but in neither case did the magnitude of the hypersecretion approach ten to twentyfold, as in our first dog. Thus we have in these findings further coroboration of Dr. Winkelstein's major thesis regarding the functional interrelations of the glands of internal and of external secretion. There can be no doubt of the importance of these interrelations and of the need for their thoroughgoing physiological investigation.

SECTION III—*Nutrition*

Ketosis as Measured by the Ketonemia Following Fat Ingestion by Obese and Non-Obese Patients*

By

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INTRODUCTION

THE ketone or "acetone" bodies in the blood are apparently end products of incompletely oxidized fatty acids. These substances are acetoacetic acid, B-hydroxybutyric acid and acetone in order of formation. They occur in the blood at a low level under normal conditions and in the fed subject seldom exceed 1 mg. in 100 c.c. The term "ketosis" is used to imply an abnormal accumulation of the ketone bodies in the blood (ketonemia), and an excessive excretion of the same substances in the urine (ketonuria). The determination of the blood ketones is a somewhat difficult and tedious procedure and has been but little applied to general clinical studies. As a result of this, ketonuria alone generally has been studied. There is reason to believe from the data of Allen, Stillman and

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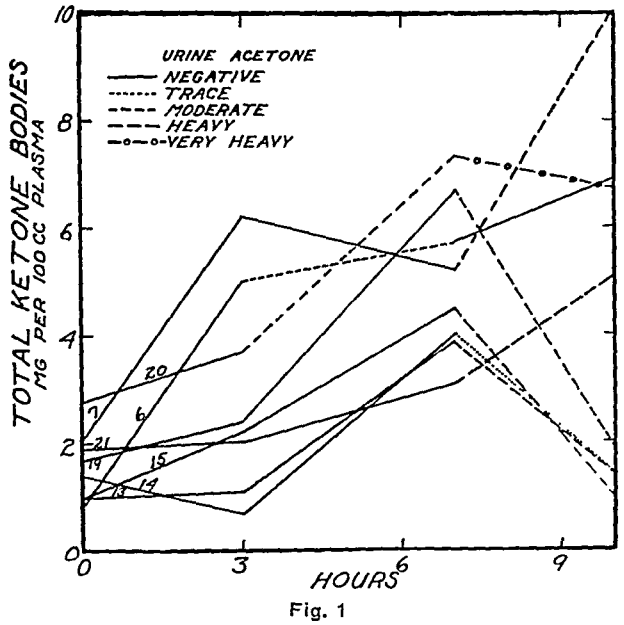


Fig. 1

Fitz (1) that this may be a poor measure of the degree of ketosis. It seemed probable that some insight might be gained into a possible abnormality in the fat metabolism of obese individuals by a study of the degree of ketonemia under certain controlled conditions.

METHODS

Fat meals were administered to fasting patients and the total ketone bodies of the blood determined at definite intervals thereafter. We were unable to control the pre-experimental diet in our patients but there is no indication that it influenced the results in our experiments. (See discussion). Five patients (Nos. 1, 2, 3, 4, 17) had been on a low fat, low caloric diet. Six of the group (Nos. 11, 12, 16, 17, 19, 20) had been eating their natural diet at home while the rest had been on the regular general diet at this Clinic. After partaking of their usual evening meal of the preceding day, no food or medication was allowed until the observations were completed.

At 6 A. M. a blood sample was drawn for a ketone body determination. Immediately thereafter 150 c.c. of 36-40% cream per square meter of body surface were given with a small amount of water. Body surface was calculated from the formula of DuBois (2) using the observed body weight. Blood samples (20 c.c.) were taken in all of the experiments 3 and 7 hours *post cibum* and in the later experiments 10 hours after the cream was administered. The total ketone bodies were determined on the serum by Van Slyke's method (3). Urine was collected in some experiments over the periods between each blood sample, from 0-3 hours, 3-7 hours and 7-10 hours, and examined for acetone and acetoacetic acid by Rotheras' and Gerhardt's tests respectively.

Most of the patients had been in bed before the test. During the first experiments some of the patients were allowed to walk about the corridors or sit in chairs, but we noticed Gemmill's (4) report that subjects on a low carbohydrate diet show a rise in blood acetone following exercise, and the majority of the experiments were carried out under approximately basal conditions.

EXPERIMENTAL MATERIAL

The patients who were submitted to our "fat metabolism test" were selected, except for certain minor details, only insofar as they were obese or not obese and that they had no other obvious metabolic disorder. In the administration of a fat meal, one becomes directly interested in the patient's ability to digest and absorb fat. Patients with clinical symptoms or laboratory findings suggestive of pancreatic, biliary or gastro-intestinal disease were excluded from our summary of data on obese and non-obese subjects. None of the subjects complained of untoward symptoms during the experiment.

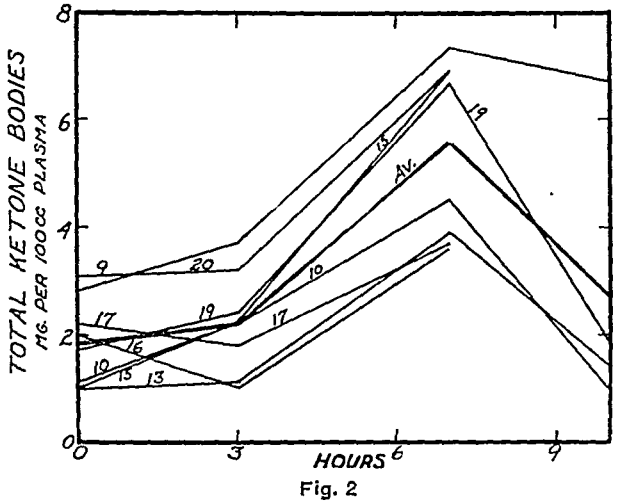


Fig. 2

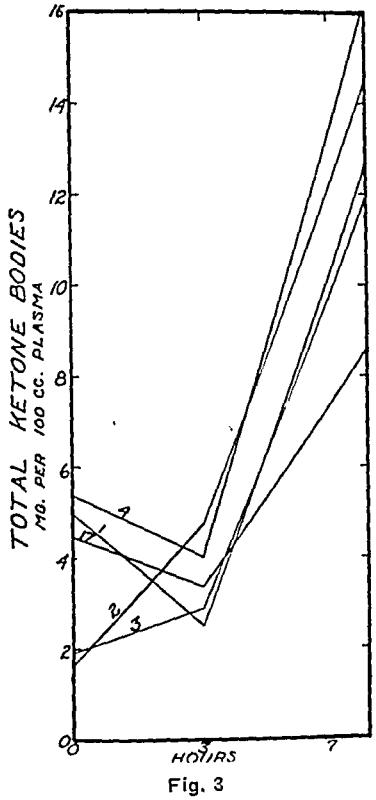


Fig. 3

RELATION OF KETONURIA TO THE DEGREE OF KETONEMIA

In the patients (Fig. 1) in which urine specimens were collected and tested all tests for diacetic acid except two were negative. Acetone was of course also present in these two specimens, as well as others. Figure 1 indicates the relation of the ketonuria to the

serum ketone concentration. In only one experiment did an acetonuria appear in the urine collected at 3 hours *post cibum*. In all of the other patients acetone appeared in the 3-7 hour urine and was still present in the 7-10 hour urine.

We have already noted that the relation between blood and urine ketones has not been studied and the

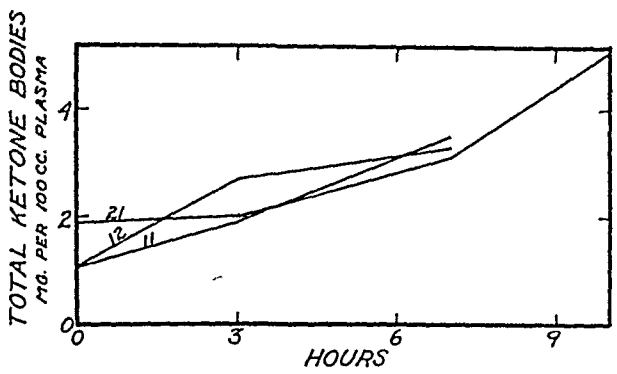


Fig. 4

data of Allen, *et al* (1) indicate a peculiar lack of association between the two. In no patient did acetonuria occur unless the serum ketone level was observed above 3.1 mg. per 100 c.c.. The apparent average blood ketone level at the time of the initial appearance of the acetonuria was for all patients 4.5 mg. per cent. The existence of a renal threshold is of course implied. At levels of the blood ketones higher than 4 mg. per 100 c.c. acetonuria was continuously observed. In the three patients with an acetonuria between the 7th and 10th hours while the blood ketones were falling to low levels it is probable that the acetone in the urine was excreted while the serum ketone concentration was above 3 mg. per cent.

RESULTS IN NON-OBESE PATIENTS

The eight subjects in the non-obese group ranged in age from 26 to 66 years. The curves of the plasma acetone bodies for this group forms Figure 2. It will be observed that the average fasting blood ketone level is 1.86 mgm., which is in accord with the figures found by Marriott (5). At the end of 3 hours, the ketone bodies rose but little. However, at the end of 7 hours there is an average increase of 3.8 mgm. per 100 c.c., with a maximum rise in one case of 5.8 mgm. The only drop below the blood fasting level occurred in two patients (Nos. 16 and 17) after three hours. At the end of 10 hours, in nearly every case, the curves were approaching their fasting levels.

RESULTS IN OBESE PATIENTS

These subjects represented a group of individuals ranging in age from 28 to 52 years. In all patients studied in this group the fat was generally distributed. Four of the group were from 40 to 100 lbs. over their normal standard weights. One had dieted rigidly and was at the time of the experiment only 20 lbs. overweight. Previous to the experiments, all the patients were on a low fat, low calorie diet.

The blood ketone curves of the obese patients are depicted graphically in Figure 3. One will readily recognize the great difference in the contour of the curves representing the majority of the obese from those which are representative of normal subjects (Fig. 2). In the case of the obese, the average fasting blood ketone level is 3.6 mgm., about twice the fasting level of the average normal. As in the case of the normals, there is no considerable change after 3 hours. At the end of 7 hours there is an increase of 9.1 mgm., per 100 c.c. which is nearly 3 times that obtained for

TABLE I

Clinic No.	Experimental No.	Age	Sex	Standard Weight lbs.	Present Weight lbs.	Surface Area sq. m.	Am't Cream Given c.c.	Status During Test	Previous Diet	B.M.R. %	Remarks
9201	1	28	F	137½	237¼	2.13	318	Bed	Low fat	—5	Obese
9178	2	52	F	135	219	1.96	294	Up and active	Low fat	—3	Obese
7039	3	38	F	131	195	1.90	285	Quiet in chair	Low fat	—1	Obese
9181	4	36	M		218	2.12	318	Bed	Low fat	—9	Obese
9223	6	20	F	130	136	1.68	252	Up and active	General		Normal
9233	7	56	F	129	116	1.41	216	Bed	General	—2	G. B. disease—underweight
8126	9	65	M	145	160	1.88	288	Up and active	O. P.		Arteriosclerosis—normal weight
9186	10	46	M	190	210	2.14	321	Up and active	General	—3	Hypertension—normal weight
5464	11	28	F	135	169	1.83	275	Bed	O. P.	—4	Obese
5230	12	62	F	148	194	1.90	285	Up and active	O. P.	—5	Obese—gall bladder
9251	13	26	F	135	120	1.58	238	Bed	General	—12	Gastritis—normal weight
9245	14	38	M	159	171	1.91	285	Bed	General	—8	Acromegaly—normal hgt. and weight
9252	15	25	M	137	135	1.66	249	Bed	General	—16	Normal
5450	16	60	F	118	154	1.75	262	Active	O. P.	—2	Chronic bronchitis
5453	17	52	F	118	131	1.65	247	Active	O. P.	—6	Hypertension
6359	18	51	F	141	159	1.72	250	Bed	Low fat	—4	Obese
3685	19	66	F	152	160	1.80	252	Bed	O. P.		
5190	20	34	F	150	150	1.83	270	Bed	O. P.	—10	Adenoma right breast
5161	21	25	F	135	252	2.19	328	Bed	Low fat	—10	Obesity—Hypogenitalism

normals. In 3 of the patients, (Nos. 1, 4, 17), there was a fall below the fasting level after 3 hours *post cibum*. The maximum rises were respectively 13.1 mgms. and 4.1 mgm.

MISCELLANEOUS OBSERVATIONS

Observations were made on patients 6, 7 and 14 without the idea of including them in our normal or obese groups. In 6 and 7 the ketonemia was a little higher (Fig. 1) than the normals. Patient 6 gave symptoms suggestive of an endocrine disorder and patient 7 had a diagnosis of gall bladder disease. Patient 14 was a typical case in clinical appearance, of acromegaly although the usual laboratory tests were all normal. The degree of ketonemia following fat ingestion in this patient was no greater than in the normals.

We have considered three obese patients, (Nos. 11, 12 and 21) on whom the degree of ketonemia was within the normal range, separately (Fig. 4). Patient 12 had had diarrhea for 2 weeks prior to the test as a toxic manifestation of digitalization and it is possible that this hindered the absorption of the fat meal. On patient 11 the blood glucose determinations made concomitantly with those for acetone were likewise low, and we can offer no fitting explanation of either finding. Patient 21 had gained weight steadily since an ovarian operation 9 years ago, and we can only speculate as to the relation of the low acetone curve to the apparent glanular dysfunction.

DISCUSSION

It has been shown quite definitely that the ketone bodies are produced in the liver (6). Are the differences we have found between non-obese and obese subjects due to a higher fat content of the liver in the latter group? At autopsy, obese subjects generally have fatty livers but as a rule they have been suffering from some disease and probably had been given an insufficient diet preceding death which might easily be the cause of a fatty liver. We are unaware of any direct evidence on the question for man but Foster (7) has demonstrated extremely fatty livers in the remarkable obesity which follows injuries to the brain in the region of the hypophsis of the rat. Furthermore, these livers presented an exception to the usual generalization that, when the liver fat is high, the glycogen is low and *vice versa* for, with the high fat, they contained more glycogen than the livers of non-obese rats. This is important for such conditions would of necessity exist in the livers of obese humans if their livers had at all times a high fat content. If these subjects naturally have fatty livers this might account for our results as Duel, *et al* (8) have found that the ketonuria developed in the rat is greater when any amount of fat has been deposited in their liver.

If obese subjects developed a ketosis more readily than other patients, this might easily explain our results but the belief is generally held that, in obesity, the onset or severity of the ketosis of starvation is no different from that in non-obese individuals. In the absence of direct evidence upon the subject, it would seem reasonable to suppose that the ketosis in the obese, during fasting or on a high fat diet, would be greater than in the normal simply because of the nature of their metabolic mixture due to the excessive fat deposits available for oxidation. Twenty years ago Folin and Denis (9) came to the conclusion that "obesity is not a predisposing or contributing factor in the onset of the acidosis of starvation" from a study of two obese subjects and one of these developed an unusually high degree of ketonuria. Now Deuel and Gulick (10) have recently concluded that "obesity is not a predisposing cause of acidosis," but, if we examine their data on male subjects, we find two whose heights and weights indicate that they are obese. The average of the 9 fasts on these two obese subjects in comparison with the average of 13 fasts on their 3 none obese subjects, shows a ketonuria at least twice as great in the obese, commencing even on the first day. It is possible that this is the explanation of the difference in the ketonemia of obese and non-obese subjects which we have observed.

There are obviously many factors involved in the degree of ketonemia which occurs after the ingestion of fat. The occurrence of the usual non-obese results in obese subjects and *vice versa* indicates that "fat tolerance tests," as measured by the ketonemia following fat ingestion, have little diagnostic significance and at most are of physiological interest in the study of obesity.

Goldzieher, *et al* (11) have proposed a test somewhat like the one used in the present study for diagnostic purposes in disease of the anterior pituitary. Although we made no direct examination of their method, such comparison as is possible between their work and this investigation would not seem to lend support to their results. Goldzieher and his co-workers interpreted a rise in the blood acetone bodies, one and two hours following the ingestion of fat after an overnight fast, as normal. We frequently failed to obtain any degree of ketonemia within even three hours after heavy cream alone and after the addition of more carbohydrate (heavy cream contains considerable carbohydrate) to the cream we have never found any increase in the blood ketones. The investigators in question diluted the cream fed with an equal volume of milk and fed still more carbohydrate in the form of two slices of toast with an ounce of butter. A drop in the blood ketones such as they postulate after a fatty meal in persons with disease of the anterior pituitary occurred here when there was no evidence of pituitary disease, (Table I and Figures).

SUMMARY

The degree of ketonemia is a better measure of the degree of ketosis than is the ketonuria.

In obese patients the ketonemia following a fat meal is generally higher than in non-obese patients. This may be due to the easier development of ketosis in obese subjects although this view is not supported by the conclusions in the literature.

Some obese patients develop no more ketonemia following a fat meal than do the majority of non-obese patients and some normals develop a ketonemia of the obese type. Reasons for this are discussed.

The evidence at the present time does not support the view that fat tolerance tests may aid in the diagnosis of pituitary disease.

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Is Gastric Secretion or Digestion Impaired by a Mixture of Carbohydrate and Protein in the Diet?*

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EVERY era and every generation have seen "healers" prey upon the gullibility of mankind, for in nothing is the human credulousness so unbounded as in matters of health and disease. These mountebanks, to paraphrase Pliny (a), traffic with our lives to make a name for themselves through some novelty. Moreover, this was probably never truer than in our own time. Progress in medical science and invention has sharpened the wits of Man, yet popular medicine remains ridiculous because its dicta make such easy prey of otherwise intelligent people. The innate horror of sickness and death that in the Stone Age created the medicine man, that later brought the best people of France to a Mesmer, or sold the metallic tractors of an Elisha Perkins (b) to the founders of our own nation, today supports in kingly fashion the lecture tour of one diet faddist or another, because emotionally we are still walking with Cro-Magnon man.

These various fads may have no more foundation in science than the cabbage and gibberish of a Cato the Censor (c), or the abracadabra of a Serenus Samonicus (d); nevertheless, scientific medicine ought not to expect to outlaw them by the puissance of its established authority or by a barrage of invective. The latter is too like professional bigotry, and the former has too often been directed against genuinely outstanding medical figures to be entirely free from suspicion. From the professional persecution of Vesalius to the Academic resentment against Pasteur, medical history is not wanting in injustices of our body scientific. It remains, therefore, for Medicine to examine these fads in proper investigations and to establish or to deny their claims through legitimate studies.

A diet fad today enjoying a great vogue is founded upon the idea that the stomach secretions are unfavorably affected by a mixed carbohydrate-and-protein diet. It is implicit that such a diet would produce abnormal digestion and subsequent harm to the economy. The

*Mr. Samuel S. Fels has not only made the grant under which the studies were originated and carried through, but at weekly conferences contributed much to the actual work.
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(a) Pliny the Elder, Gaius Plinius Secundus (23-79 A. D.), in his "Natural History," decrying some of the medical practices of the period, writes: "Nec dubi e omnes istos fama nouitate aliqua aucupantes animas statim nostras negocinri." (There is no doubt that those who seek to be in vogue by some novelty or other, acquire it at the expense of our lives). Caii Plinii Secundi: Naturalis Historiae Libra XXIX.

(b) Elisha Perkins, born in 1741, was a Connecticut physician who devised two metal rods (Perkins Patent Tractors) which would draw off disease from the body. He numbered among his purchasers some of the contemporary leaders of the country. "Fads and Quackery in Healing," by Morris Fishbein. Blue Ribbon Book, Inc., N. Y., pp. 9-12, 1932.

(c) Cato the Censor or the Elder (234-149 B. C.). In his book, "De Agricultura," prescribed cabbage, the favorite vegetable of the Pythagoreans, for all ills. He ordered it internally, both raw and cooked, and as a poultice for sores; he declared it would cure even cancer and he injected its juice into sinuses and fistulae by means of a syringe composed of a bladder tied to a reed. Medical History From Earliest Times. Ed. Dawson Withington, Scientific Press, London, p. 71, 1894.

(d) "With the passing of Galen at the end of the second century, the thread of rational medicine snaps. Medicine now strips at a ghostly loom, producing charms and amulets, and the dozen of the age is the Abracadabra. The book De Medicina Praecepta which wound out to fifteen hundred hexameters entangled the profession and public alike. Classics which should have been immortal have perished, while the rubbish of Serenus Samonicus has survived, for its formulae were repeated in countless incantations and the sick wore the magic word—Serenus Samonicus explained that abracadabra must be written out on the first line, and a letter dropped with each succeeding line thus forcing the demon of the disease gradually to release its grip upon its victim." Victor Robinson, The Story of Medicine, Tudor Publishing Co., N. Y., pp. 193-194. See also Quinti Sereni Samonici De Medicina Praecepta Salubertima

whole idea originates, obviously, in the isolated scientific fact that proteins require a relatively high gastric acidity for initial digestion, while carbohydrates need an alkaline medium. Out of this has been built a

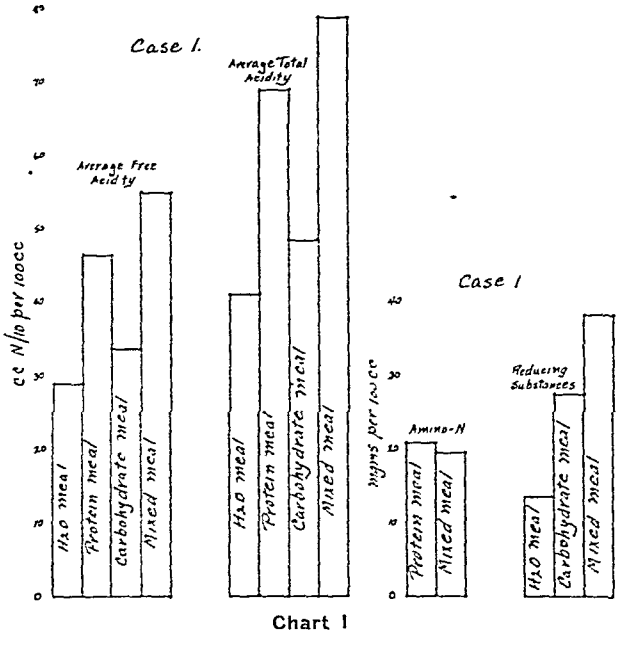


Chart I

series of "do's and don'ts" which is presumed to separate the groups of foodstuffs.

Rehfuss (1), realizing the importance of investigating the claims of such a diet cure, recently published, for fifty cases of chronic illness, the gastric acid response to a protein, a carbohydrate, and a mixed meal. He was unable to detect any notable difference in the average acid response to any of these meals. Independently, about two years ago, we began a detailed study of the gastric response to similar meals in a group of healthy individuals in order to test the validity of forbidding such mixtures in the diet. We

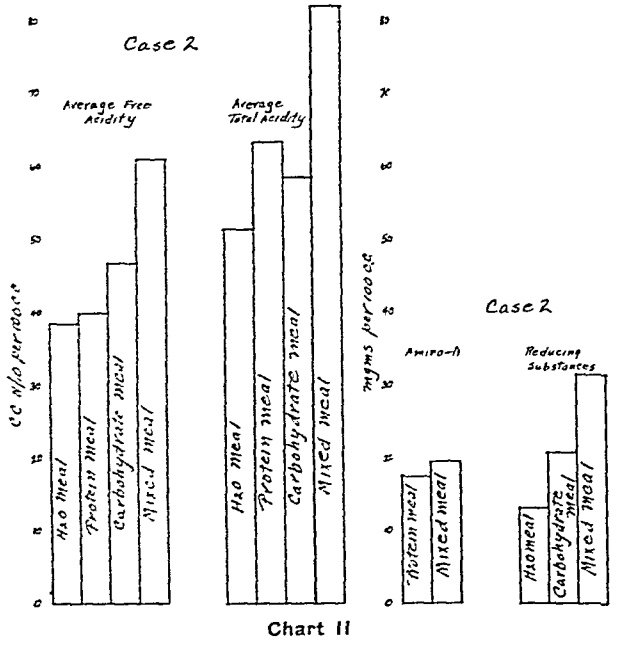


Chart II

felt that because of the variations possible in test-meal studies (the result, no doubt, of the fact that such studies now represent secretion concentrations of *unit volume* and *not unit time)* it would be better to obtain the average figures for each type of test meal through repeated studies with the meal on a small group of patients than to depend upon single observations on a large group. Five cases were so studied: four with normal secretory responses and one with a gastric anacidity. The fractional method of gastric analysis was employed throughout. The test-meals consisted of 300 c.c. of distilled water alone; of 9 grams of egg albumen (Merck); of 15 grams of soluble starch (Merck); and, finally, of a mixture of the two dissolved in the always constant volume of 300 c.c. of distilled water. Our studies included a titration of free hydrochloric acid to dimethyamidoazobenzol (Topfer) and a titration of total acid to phenolphthalein. We also made determinations of the hydrogen ion concentration with the quinhydrone electrode; of total

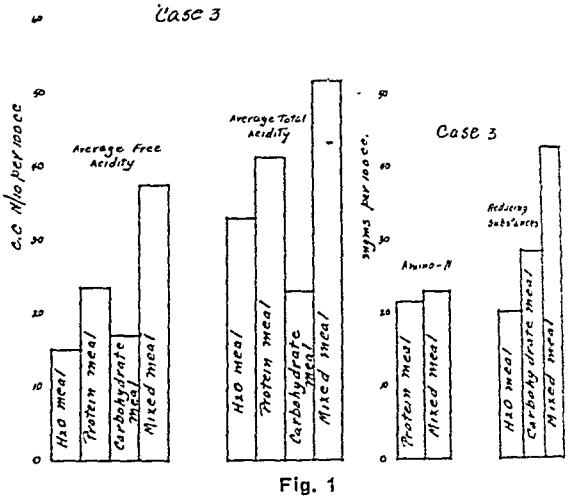


Fig. 1

chlorides by a modification by Wilson and Ball (2) of the Van Slyke method; of pepsin by a slight modification of the method of Polland and Bloomfield (3). These data upon analysis help us to answer the problem of the interference with the proper gastric secretion by food mixtures. We also tried to determine whether the intragastric decomposition of either carbohydrate or protein was retarded by their mixture in the diet. Therefore, we investigated the change in concentration of reducing substances in the gastric samples, after the starch and mixed meals, by the Hagedorn-Jensen method (4) for blood-sugar. We determined protein cleavage by the amino-nitrogen concentration, with the Van Slyke (5) amino-nitrogen apparatus, following the protein and mixed meals. Numerous studies were done simultaneously on the blood, urine, and saliva, in order to study the secondary general effects of gastric secretion and digestion, and the motor effects were subsequently investigated by means of the X-ray. We are limiting ourselves, however, at this time to the gastric findings only.

AUTHORS' STUDY

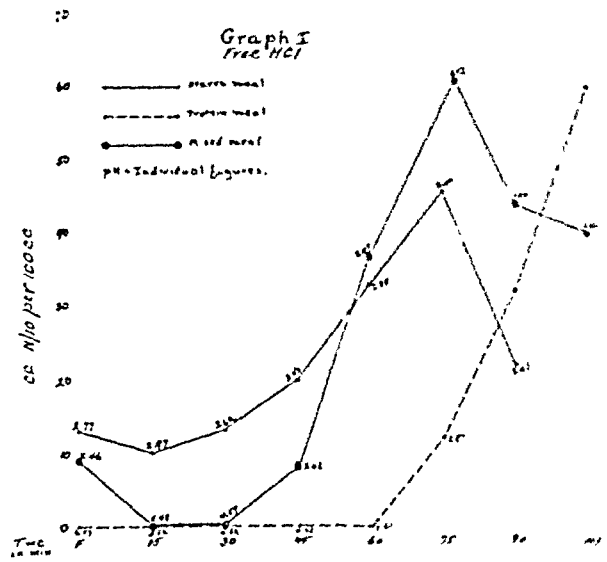
This report is based upon more than 6,000 determinations made on over 900 gastric specimens obtained

from five patients in successive studies with the meals outlined above.

Chart I gives the average of all the figures obtained for each gastric constituent for each of the test-meals employed. In determining these averages, the fasting values have been eliminated from the calculations because they were not directly concerned with the response to the various meals, and we felt that by eliminating them we could obtain a truer figure of the response.

We included the plain-water meal in our studies in order to show that water alone produces an adequate secretory response. That water may do this in man, has been pointed out by Ivy (6) and has recently been reiterated by us (7). Particularly interesting is the fact that the carbohydrate meal alone may call forth even a greater secretion of gastric acid than the water alone. In one instance, Case 2, the average free acidity of the carbohydrate-water meal was more than 20% greater than that provoked by the pure water. In Case 2 it also appears that the average response in free acidity was even greater than that obtained with the protein meal. This, however, we believe is more apparent than real, because if we remember the acid-combining power of the protein, we can thereby account for some of the free acid in the total acid figure. It will be noted that in every instance the average acid response obtained with the mixed meal was higher than that obtained from the protein meal alone. The average total chloride figures generally followed the acid curves. The fact that we occasionally obtained lower pH average readings with the water and water-carbohydrate meals than with the protein and mixed meals, in spite of the higher titratable acidity provoked by the latter, is not surprising when we consider the combining factor of the proteins present and the increased buffer action. In most cases the average pepsin concentration was higher with the water-carbohydrate meal than when protein was present.

More striking still, from the standpoint of our thesis, are the individual acid curves. Graph I illustrates this point. The protein in the meal, combining with the available free acid during the earlier periods of digestion, permits the reaction of the gastric contents to remain more favorable for amylolytic action



Graph 1. Curves of free acidity obtained with carbohydrates, with protein, and with mixed meal, illustrating how the presence of protein in the diet would actually favor continued carbohydrate digestion in the stomach. This is evidenced not only by the prolongation of the period of low titratable acidity following the ingestion of food, but also by the more favorable hydrogen ion concentration that would more likely permit continued amylolytic activity.

during a longer time than when carbohydrate alone is ingested. *It appears, therefore, that continued salivary digestion in the stomach would be favored rather than hindered by the admixture of carbohydrate and protein.* It is interesting to note that the highest average concentration of reducing substances for the carbohydrate meals (46.12 mgs. per 100 c.c.) in the gastric contents was obtained in the anacid case. This is, of course, explicable on the basis of better and more continued salivary action in the absence of all gastric hydrochloric acid. (We feel that the rest of the material on the anacid case is irrelevent to the main point under discussion here and have, therefore, omitted it).

The average amino-nitrogen concentration was as great in the meals containing a mixture of carbohydrate and protein as in those containing protein alone,

TABLE I

Average Values of Four Fractional Studies for each Test Meal

Meal 300 c.c.	F. A. c.c.	T. A. c.c.	Chl. c.c.	pH.	Pepsin	Amino Acid N.	Reducing Subs.
CASE 1							
H_2O	28.8	41.2	92.7	2.13	39.5		13.87
Egg White 3%	46.3	68.7	104.8	2.05	45.2	20.80	
Starch 5%	33.9	48.4	88.4	2.25	50.1		27.62
Mixed Meal	54.6	78.8	114.0	2.17	41.6	19.87	38.08
CASE 2							
F. A. c.c.	T. A. c.c.	Chl. c.c.	pH	Pepsin	Amino Acid N.	Reducing Subs.
38.6	51.6	103.7	1.90	65.6		15.46
39.9	62.3	114.1	2.05	44.3	17.75	
16.6	38.3	96.8	1.95	41.4		29.58
60.7	83.0	113.2	1.81	76.0	19.24	33.42
CASE 3							
H_2O	15.0	32.7	65.2	3.10	12.1	21.43	20.93
Egg White 3%	23.4	40.9	67.8	2.47	41.1		
Starch 5%	16.4	23.3	59.1	2.78	40.1		28.14
Mixed Meal	37.7	51.8	76.3	2.60	38.5	22.62	42.61
CASE 4							
25.7	35.9	64.7	2.72	25.7		4.47
33.2	58.0	104.5	2.50	52.7	26.53	
31.8	45.8	71.5	1.91	54.1		22.10
40.8	65.3	87.8	2.12	82.2	27.42	41.49

F. A.=Free HCl expressed as N 10 per 100 c.c.
T. A.=Total Acid expressed as N 10 per 100 c.c.
Chl.=Total Chloride expressed as N 10 per 100 c.c.

Pepsin expressed as mgms. of egg white digested by 1 c.c. gastric [illegible]
Amino N. expressed in mgms. per 100 c.c.
Reducing Subs. expressed in mgms. per 100 c.c.

while the reducing substances in all the cases showed a higher concentration in the mixed meal than in the straight starch meal, again emphasizing the greater carbohydrate splitting in the stomach in the presence of protein. These findings show clearly that neither protein nor carbohydrate splitting was impaired in the slightest when ingested in combination.

DISCUSSION

Since our experimental data show clearly that there is impairment neither of gastric secretion nor of gastric digestion following the ingestion of a mixture of carbohydrate and protein, we may still ask for an explanation of the many "cures" reported for a diet in

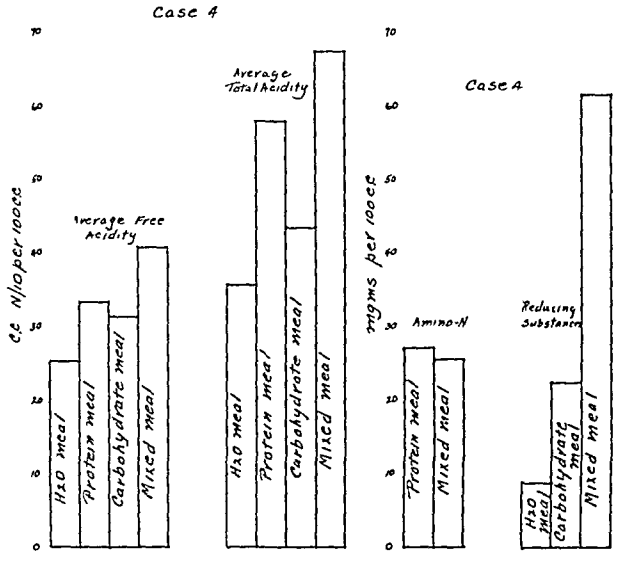


Fig. 2

which these food groups have supposedly been separated. The answer lies very probably in the natural improvement of any diet over the original unintelligent eating habits of a great many of us. These habits, characterized as they are by gluttony; an excessive consumption of highly concentrated foods, especially carbohydrates; and a failure to exercise properly result in an atonicity of skeletal and intestinal musculature; excessive fat deposits; flatulence; and constipation. If we now replace the highly concentrated starches almost entirely by the 3% and 5% starch vegetables and the 5% and 10% fruits, satiation will be achieved with a much smaller caloric intake. In this way, the pabulum for the fermentative organisms in the bowel will be diminished, and their growth will be discouraged, with a consequent reduction in flatulence. With the additional bulk in the diet, the atonic bowel will be encouraged to better bowel function without the use of laxatives, a weight loss will follow the smaller caloric intake, and as a result of all these an inevitable improvement in the condition of the patient.

Such an explanation for a special therapy is embarrassingly simple and would, naturally be completely unimpressive to an Age so thoroughly complex. Therefore, the talk is of "impaired gastric secretion," and "gastric digestion," etc., which is highly significant, but quite inappropiate phraseology. One must recognize too, that very harmful results may follow such a diet in patients with gastritis, duodenitis, an irritable colon, or a true colitis—results which will, of course, remain unpublicised.

SUMMARY AND CONCLUSIONS

Five people, free of any organic gastro-intestinal disease, were studied by repeated fractional gastric analysis following meals of distilled water, a pure carbohydrate, a pure protein, and mixtures of the two. Four had a normal gastric acid response and one was an achlorhydric. The studies were done in order to test the validity of the claims made that mixtures of protein and carbohydrate interfere with proper gastric digestion. The gastric secretory studies included the usual titration of acidity to Topfer's and to phenolphthalein, hydrogen ion determinations, total chlorides, and quantitative pepsin. Gastric digestion was followed by quantitative determinations of reducing substances and amino-nitrogen in the separate fractions. More than 6,000 determinations were made on over 900 fractional specimens in the course of the studies. The results showed that:

(1) Mixtures of carbohydrate and protein in the test meal do not, in any way, interfere with gastric secretion.

(2) Not only do these mixtures not interfere with gastric digestion, *but that carbohydrate digestion in the stomach is prolonged and encouraged by its mixture with protein.* This is probably brought about by the more favorable reaction for continued ptyalin activity in the stomach as a result of the acid combining power of the protein. The same would be true following any regurgitation of pancreatic amylase from the duodenum.

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SECTION V—*Therapeutics*

I. Effect of Acetylsalicylic Acid Upon Gastric Activity and the Modifying Action of Calcium Gluconate and Sodium Bicarbonate*

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LITTLE literature is available regarding the action of salicylates upon gastric secretion, which is rather odd when one considers how widely such medication is employed. Klockman (1) concluded from three experiments upon two dogs which received a test breakfast and 0.5 gm. of sodium salicylate that sodium salicylate decreases gastric secretion and acidity. Leichtentritt (2), on the other hand, reported a rise in gastric secretion in one dog receiving a meal of meat and milk to which was added 0.5 gm. of sodium salicylate. Veil and Graubner (3) observed human cases in which one dose of salicyl compound inhibited the formation of hydrochloric acid. The results of Morris and Graham (4) were inconclusive. Although it is believed that salicylate medication is a cause of gastric anacidity (5), there is no reliable clinical evidence supporting this belief. For example, no one has made control gastric analyses prior to salicylate medication and then has repeated the analyses afterwards in patients.

On the contrary, the use of sodium bicarbonate for reducing local gastric irritation and for preventing the acidosis secondary to salicylate therapy is well known (4, 6). The ameliorating influence of sodium bicarbonate on certain of the undesirable features of acetylsalicylic acid administration has been confirmed recently by Thompson and Dragstedt (7), who also found that calcium gluconate possessed similar, if not greater effects. Certain evidence suggested to these authors that the action of calcium in protecting against salicylism might be due to a systemic influence, such as the protective influence of calcium against carbon tetrachloride poisoning (8). Both sodium bicarbonate and calcium gluconate appreciably decreased local gastro-duodenal irritation and the incidence of ulceration caused by acetylsalicylic acid alone.

Our investigation was undertaken to ascertain the effect of acetylsalicylic acid on gastric secretion and emptying time and to determine if the protective action of sodium bicarbonate and calcium gluconate against the gastro-duodenal irritation associated with acetylsalicylic acid medication may be explained by detectable changes in gastric secretion and motility.

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METHODS

The effect of single doses of acetylsalicylic acid upon gastric activity was determined on normal human subjects, normal dogs and upon dogs with pouches of the entire stomach. The effect of prolonged daily administration was determined upon normal dogs and upon dogs with Pavlov pouches of the stomach.

Doses of the drug were chosen so that a single administration would not, and did not, provoke nausea and vomiting, but that on continued administration some evidence of gastro-intestinal irritation would be obtained.

Single doses of acetylsalicylic acid: The effect of single doses of acetylsalicylic acid and mixtures of acetylsalicylic acid and calcium gluconate and acetylsalicylic acid and sodium bicarbonate was determined upon ten normal human subjects. The subjects were fasted at least twelve hours before the fractional gastric analysis was conducted upon them. A Rehfuss tube was passed to a distance which allowed the tip to reach the most dependent part of the stomach. The volume of aspirated residual contents was noted and a 1 c.c. sample was titrated with N/10 NaOH for free and total acidity using p. dimethylaminoazobenzene and phenophthalein as indicators. Basal secretions were withdrawn at ten minute intervals for thirty or forty minutes. With the establishment of a basal level of secretion, a control volume of 250 c.c. of distilled water was injected through the tube into the stomach. At ten minute intervals the entire contents of the stomach were aspirated; the volumes were noted and re-injected except for 4 c.c. samples which were kept for analysis. The sum of the volumes recovered at ten minute intervals indicated the degree of gastric retention. Relative acidities of the stomach contents were indicated by a comparison of the titrable acidity at ten minute intervals. Each subject was kept quiet and instructed not to swallow saliva during the test. When the stomach had emptied (contents less than 20 c.c.) the above procedure was repeated with 250 c.c. aqueous solutions of acetylsalicylic acid (1 and 2 gm.) and with acetylsalicylic acid (2 gm.) and calcium gluconate (1 gm.), and acetylsalicylic acid (1 gm.) and sodium bicarbonate (1 gm.).

Five normal dogs were also employed to determine the effect of single doses of aqueous solutions of the drug upon

gastric secretion. After washing the stomachs of the fasted dogs with distilled water, control determinations were made by introducing 250 c.c. of distilled water. In 20 minutes the entire contents were aspirated and replaced by a 250 c.c. aqueous solution containing acetylsalicylic acid (1 gm.) or mixtures of acetylsalicylic acid (1 gm.) and calcium gluconate (0.5 gm.) or of acetylsalicylic acid (1 gm.) and sodium bicarbonate (1 gm.). The volume aspirated at the end of 20 minutes was noted and determinations of titrable acidity and chlorides were made.

Total stomach pouch dogs: (9). The stomach pouch was washed with distilled water and a control perfusion with 100 c.c. of distilled water for one hour was made. The gastric juice was then collected for two 1 hour periods after which the pouch was washed and perfused for one hour with a 100 c.c. aqueous solution of acetylsalicylic acid (0.25 gm.) or of a similar amount of acetylsalicylic acid with calcium gluconate (0.175 gm.) or sodium bicarbonate (0.25 gm.). Following this the gastric secretion was collected again for two 1 hour periods. The 1 hour perfusates were analyzed for titrable acidity and chlorides.

Chronic acetylsalicylate therapy. To determine the effect of prolonged daily administration of acetylsalicylic acid on gastric secretion normal dogs and dogs with a Pavlov pouch of the stomach were used.

Nine normal dogs were fed a test-meal consisting of 200 gm. of food and 250 c.c. of water. Two hours later samples of the gastric contents were withdrawn by means of a stomach pump and titrated for free and total acidity. Three such control determinations on consecutive days gave similar results; the averages of which served as controls. The drug was then administered twice a day for *one month.* Three of the dogs received a total daily dose of acetylsalicylic acid of 3 gm. each; another group of three dogs each received 3 gm. of acetylsalicylic acid and 1.5 gm. of calcium gluconate while each of the last group of three received a similar amount of acetylsalicylic acid with 3 gm. of sodium bicarbonate. Weekly determinations of gastric acidity were made as described above before the drug was administered so that its presence might not alter the acidity due to its acidic properties. The dogs were sacrificed after the experiment and the incidence of gastric ulcers noted.

The Pavlov pouch dogs were standardized to a test meal of 300 gm. of food and 250 c.c. of milk to obtain their normal secretory response. Two 1 hour basal secretions were collected before, and six 1 hour secretions were collected after the meal was given. The secretions were analyzed for free and total acidity. The drugs were then given in perforated gelatine capsules 1 hour before the meal and the effect upon the secretory response was noted. The drug or "mixture" was administered daily over a period of about *three weeks.*

RESULTS

Action of single dose of acetylsalicylic acid on gastric evacuation: Analysis of the protocols (not given) of the effect of single oral doses of salicylates upon human gastric activity yielded the following findings:

One gm. of acelylsalicylic acid had no effect on the 20 or 30 minute evacuation rates in 7 out of 10 subjects, and caused definite gastric retention in 2 and slight retention in 1. Two gms. of acetylsalicylic acid had no effect on the 20 or 30 minute evacuation in 6 of the 10 subjects, and caused definite retention in 3 and slight retention in 1. Acetylsalicylic acid (2 gms.) and calcium gluconate (1 gm.) had no effect on 4, caused slight retention in 2 and definite retention in 4. Acetylsalicylic acid (1 gm.) and sodium bicarbonate (1 gm.) caused retention in 1 and increased the rate of evacuation (stomach emptied faster) in 3 out of 4 subjects. Nausea and vomiting did not occur in any of these subjects.

Acetylsalicylic acid caused definite retention whenever administered in 2 of the 10 subjects. The addition of calcium gluconate added two more subjects to the retention group while the addition of sodium bicarbonate caused an increased rate of evacuation in 3 out of 4 subjects.

It was obviously necessary to ascertain the effect of calcium gluconate alone on the rate of evacuation of water from the stomach. Calcium gluconate (1 gm.) alone was given to 6 subjects. The 20 and 30 minute evacuation rates showed that it caused definite retention in 2, no effect in 2, and slightly increased the rate of evacuation in 2.

Because the day to day variations in the rate of evacuation of water from the stomach varies in some individuals as much as 100 per cent but not more than 20 per cent in others, the precaution of determining the rate of evacuation of water on the day of the experiment prior to the giving of the drug was very important. It should be remarked that, with the exception of three subjects on one occasion each, when acetylsalicylic acid was introduced into the stomach the amount of fluid recovered at 20 and 30 minutes was practically always greater than that recovered in the control water tests. This indicates that the general trend of the effect of acetylsalicylic acid on the evacuation of the stomach is in the direction of retention and when the data is so analyzed this trend is indicated to a greater extent than that exemplified by the analysis of the data given above. The reason for this is that because of daily variations we interpreted a 10 or 15 per cent retention as insignificant. This is the only legitimate way of treating the data.

When the sums of the volumes of fluid removed from the stomach at each ten minute period during the 1½ hour water-test period and the 1½ hour drug-test period are compared, it is found that with but few exceptions a greater volume of fluid was removed from the stomach in the drug experiments (Table I). When expressed in percentage differences the results are as follows: 7 per cent more fluid was removed from the stomach when 1 gm. of acetylsalicylic acid was administered than when water alone was administered, 6 per cent more with 2 gms. of aspirin, and 33 per cent more for a mixture of acetylsalicylic acid (2 gms.) and calcium gluconate (1 gm.), while 33 per cent less was removed with acetylsalicylic acid (1 gm.) and $NaHCO_3$ (1 gm.). These figures, however, express not only the fluid retention but also the gastric secretion. This shows that when the drugs were given the general trend toward retention was accompanied by *either* a greater secretion of acid juice or mucoid dilution fluid, bile stained fluid being obtained in only twelve instances out of eighty tests.

The effect of acetylsalicylic acid upon the rate of gastric evacuation was also studied on five normal dogs. The average effects of 15 determinations at a 20 minute interval after introduction of the fluid into the stomach are shown in Table II. It is shown that at twenty minute intervals acetylsalicylic acid (1 gm.) caused a 27% decrease in the rate of gastric evacuation when compared with the rate of evacuation of water. The values for acetylsalicylic acid (1 gm.) and calcium gluconate (0.5 gm.) show a 38 per cent decrease while acetylsalicylic acid (1 gm.) and sodium

TABLE I

*Effect of Single Doses of Salicylate Upon the Emptying Rate and Acidity of the Gastric Contents in the Normal Human Subject**

Drug	Total volume recovered			Acidity (mgm. HCl / c.c.)		
	H_2O (c.c.)	Drug (c.c.)	Evacuation % + incr. — decr.	H_2O	Drug	% change + incr. — decr.
Acetyl salicylic (1 gram)	486	522	—7%	0.1473	0.1522	+27.2%
Acetylsalicylic (2 grams)	498	529	—6	0.1299	0.1574	+58.5
Calcium gluconate and acetylsalicylic acid	411	747	—81.9	0.0947	0.1407	+48.6
Acetylsalicylic acid (1 gram)** $NaHCO_3$ (1 gram)	338	226	+33	0.1503	0.1174	—21.1

*Averages of ten normal human subjects.
**Averages of four normal human subjects.

bicarbonate (1 gm.) show an increase of 12 per cent in the rate of evacuation when compared with water.

Action on gastric acidity: Our data on normal human subjects and normal dogs does not warrant any conclusions regarding the action of the drugs employed upon gastric HCl secretion. This is because of the individual variation in the rate of emptying of the stomach because of the inadequacy of the size of the dose that can be employed due to the insoluble nature of the acetylsalicylic acid, because of the acidity imparted by the drug *per se* and, finally, because of the buffer action of the calcium gluconate and sodium bicarbonate administered with the drug.

These results, therefore, indicate only the effect of the drugs upon the acidity of the *stomach contents* irrespective of the cause. In ten normal human subjects a single oral dose of acetylsalicylic acid (1 gm.) caused an average increase in *total titrable acidity* of 27.2 per cent over the water controls. Two gms. caused a 58.5 per cent increase. Acetylsalicylic acid (2 gms.) and calcium gluconate (1 gm.) caused a 48.0 per cent increase. Average results on four subjects, as might be readily predicted, showed that acetylsalicylic acid (1 gm.) and sodium bicarbonate (1 gm.) caused a 72.1 per cent decrease in the total titrable acidity as compared with the water controls.

Averages of fifteen determinations on five normal dogs (Table II) showed that the acetylsalicylic acid (1 gm.) caused an increase of 55 per cent in the total acid and 45 per cent in the total chlorides, the addition of calcium gluconate (0.5 gm.) resulted in an increase of 97 per cent in total acid and 87 per cent in total chloride, while the addition of sodium bicarbonate (1 gm.) to the acetylsalicylic acid (1 gm.) resulted in a 49 per cent decrease in titrable acidity while the total chlorides were increased 41 per cent. The percentage changes are relative to similar stimulation with distilled water. The free chloride determinations were decreased with the addition of calcium gluconate and sodium bicarbonate. This is due to the neutralizing action of these substances upon the acid in the stomach.

TABLE II

*Effect of Single Oral Doses of Salicylate Upon the Rate of Evacuation and Acidity of the Contents of the Stomach of the Normal Dog**

Drug	Volume recovered in 20 min.			Total acid (mg./100 c.c.)			Chloride (mg./100 c.c.)		
	H_2O (c.c.)	Drug (c.c.)	Evacuation % + incr. — decr.	H_2O	Drug	% Change	H_2O	Drug	% Change
Acetylsalicylic acid	128.6	162.8	—27%	104.4	162.1	+55	119	173	+45
Calcium gluconate and acetylsalicylic acid	75.2	159.5	—38%	87.2	172.3	+97	99.5	185.9	+87
Acetylsalicylic acid and $NaHCO_3$	124.6	109.5	+12%	78.7	39.9	—49	93.7	132.4	+41

*Averages of three determinations on five dogs (15 determinations on each drug)

TABLE III

*Local Effect of Salicylate Perfusion on Chloride Secretion in Dogs with Pouches of the Whole Stomach**

Drug	Total chloride (mg./100 c.c.)			Acidity (mgm. HCl / 100 c.c.)		
	H_2O Control	Drug	Change % + incr. — decr.	H_2O Control	Drug	% + incr. — decr.
Acetylsalicylic acid	93.47	100.01	+7.5	68.76	47.77	—30.5
Acetylsalicylic acid plus calcium gluconate	71.54	91.70	+28.1	5.1	24.7	+384.7
Acetylsalicylic acid plus $NaHCO_3$	72.20	70.18	—2.5	69.6	71.59	+2.1

*Averages of three perfusions with each drug (100 c.c. solutions were perfused for 1 hour)

The effects of single hourly perfusions of aqueous solutions of salicylates through whole stomach pouches of dogs on total chloride output are shown in Table III. These results indicate whether the drug has a true local "secretagogic" action. Here the factor of the emptying rate has been overcome while a determination of the chlorides indicates the relative ratios of

TABLE IV

*The Effect of Daily Administration of Salicylate Over One Month Upon the Gastric Acidity in the Normal Dog**

Drug	Total acidity (mgm./c.c.)		
	Basal	Drug	Change % + incr. — decr.
Acetylsalicylic acid	0.0548	0.0957	+74.6%
Calcium gluconate and acetylsalicylic acid	0.0619	0.0777	+25.5
Acetylsalicylic acid plus $NaHCO_3$	0.0437	0.0000	—100.0

*Averages of three dogs on each drug.

chloride secretion by the stomach in response to distilled water and then to an aqueous solution of the drug. The results show that perfusion with an aqueous solution of acetylsalicylic acid (0.25 gm.) for one hour results in a 57.5 per cent increase in the total chloride over a similar perfusion with water. Perfusion of acetylsalicylic acid (0.25 gm.) and calcium gluconate (0.17 gm.) produced an increase of only 28.1 per cent while acetylsalicylic acid (0.25 gm.) and sodium bicarbonate (0.25 gm.) produced a relative increase of only 5.5 per cent in the total chloride as compared with water alone. The gastric secretion collected for two 1 hour periods after the perfusion with water and then the salicylate solutions showed no significant differences. This was probably due to the inadequacy of the dose which was limited by the solubility of the drug. The data show that none of the solutions stimulated gastric secretion by local contact with the stomach. The increase in total chlorides being due to the secretion of a mucoid diluting fluid, which shows that acetylsalicylic causes more mucoid secretion to be formed than the acetylsalicylic acid and calcium gluconate mixture and that the acetylsalicylic acid and sodium bicarbonate caused the least formation of mucoid diluting secretion. It was impractical to assay for mucin, since the calcium gluconate precipitated it out of solution in the stomach.

Thus, these results on a pouch of the entire stomach show that acetylsalicylic acid by local contact with the stomach does not increase the output of hydrochloric acid. It does cause an increase in the secretion of a diluting fluid which generally occurs when the stomach is irritated. On this basis, the results show that sodium bicarbonate and calcium gluconate decrease the local irritative action of acetylsalicylic acid on the stomach.

Chronic daily salicylate medication: The average effects of daily oral administration of salicylates to the normal dog (3 dogs) over a period of one month are shown in Table IV. Acetylsalicylic acid (3 gms. per day) showed an average increase of 17.4 per cent in the total titrable acid above the control two hours after the meal. On a similar amount of acetylsalicylic acid given with calcium gluconate (1.5 gms.) there was only a slight average increase of total acidity (2.7 per cent) while with sodium bicarbonate (3 gms.) and acetylsalicylic acid (3 gms.) the average total acidity was actually depressed (27.1 per cent) below the control average. On autopsy two out of three dogs receiving acetylsalicylic acid alone had an ulcer, two out of three receiving acetylsalicylic acid with sodium bicarbonate had an ulcer, and one out of three receiving acetylsalicylic acid with calcium gluconate had an ulcer.

These results show that the continued daily administration of acetylsalicylic acid over a period of a month in the doses used causes an increase in the gastric secretory response to a test-meal. The addition of calcium gluconate prevented this increase; whereas, the addition of sodium bicarbonate resulted in a decreased secretory response to the test-meal.

In the Pavlov pouch dogs (Table V) daily oral administration of acetalsalicylic acid (0.2 to 0.25 gms. per kilo) for about three weeks caused an average increase in the volume of the gastric juice collected of 58.1 per cent with an average increase of the total acid output of 55.8 per cent above the control values. The augmentation was not evident until 3 or 4 days after medication was instituted, a maximum being reached at about 10 days. The secretion returned to normal about a week after withdrawing the drug. Administration of calcium gluconate (0.1 to 0.125 gms. per kilo) with the acetylsalicylic acid over a similar period of time caused an average increase of 23.3 per cent in the volume and an increase of 24.2 per cent in the acidity of the gastric secretion. When sodium bicarbonate (0.2 to 0.25 gms. per kilo) was given with the acetylsalicylic acid, the volume was decreased to 17.1 per cent, the total acid was decreased to 17.2 per cent below the control values.

Thus, the results on Pavlov pouch dogs are analogous to those obtained on the foregoing group.

It should be noted that in the dogs receiving daily acetylsalicylic acid medication, vomiting was evidenced on about the third day and continued intermittently for about ten days. When vomiting occurred, of course, the results for that day had to be discarded, though as a rule the meal was ingested later. Under such conditions it is well known that gastric secretion is depressed and such secretory results are not reliable. When calcium gluconate was given, vomiting was not frequent in its occurrence and did not appear until later, the sixth day, and the dogs also ate their food more quickly. Sodium bicarbonate also ameliorated the symptoms of partial anorexia and vomiting, but not so definitely as calcium gluconate. Our observations on the effect of calcium gluconate and sodium bicarbonate on the time of occurrence of vomiting are at variance with those of Thompson and Dragstedt (7), who observed no significant influence of the two "protectives" on the time of onset and frequency of vomiting. But they administered larger doses of acetylsalicylic acid, and our dogs were obviously, because of the nature of the experiments, under close daily observation, in the case of the Pavlov pouch dogs under observation for eight hours daily.

DISCUSSION

The results show that acetylsalicylic acid in single doses (1-2 gms.) in water causes a definite gastric retention in some human subjects and an increase in the titrable acidity of the gastric contents in all. This re-

tention and increase in titrable acidity was also observed in five normal dogs. When the drug was given over an extended period to dogs, a definite increase in the total output of HCl occurred in Pavlov pouch, as well as normal dogs, when a test-meal was fed.

Since in Pavlov pouch dogs the drug does not come into direct contact with the mucosa of the pouch, the augmented secretion of acid observed can only be due to reflex excitation or to circulating substances. That the augmented secretion is not due to local contact of the drug with the gastric mucosa is further shown by the failure of the pouch of the entire stomach to be stimulated by perfusion with the drug, although a portion of the drug was absorbed by the gastric mucosa. To determine whether the drug acts predominately through the reflex or the humoral mechanisms would constitute a prolonged and difficult study. Whichever mechanism is involved, it is influenced in an accumulative manner, since a definite increase in production of hydrochloric acid is not evident until several days after medication is started.

In regard to the ameliorating action of sodium bicarbonate and calcium gluconate on the gastric disturbances caused by acetylsalicylic acid, the results show that sodium bicarbonate decreases the gastric retention and the total titrable acidity of the gastric contents when given with single doses of acetylsalicylic acid more effectively than calcium gluconate. Also, sodium bicarbonate when given daily with acetylsalicylic acid over a prolonged period prevents the increased gastric secretory response to a test-meal more effectively than calcium gluconate. The same is true when one uses the amount of diluting secretion formed by the gastric mucosa as a criterion of irritation, *i.e.*, sodium bicarbonate reduces the irritation of the gastric mucosa by acetylsalicylic acid more than calcium gluconate. Further, less absorption of acetylsalicylic acid by the gastric mucosa occurs when sodium bicarbonate is used with the drug than when calcium gluconate is used. These observations indicate that sodium bicarbonate should be more effective in ameliorating the local irritative effects of acetylsalicylic acid on the gastro-duodenal mucosa than calcium gluconate. In fact, one may account for the ameliorating action of sodium bicarbonate entirely on the basis of the effects observed in this study; this is not the case for calcium gluconate. Yet, it would appear from our observations, which, as far as they go, confirm those of Thompson and Dragstedt, that calcium gluconate is as effective as sodium bicarbonate, if not more so, in ameliorating gastro-duodenal irritation, and that the ulcers, which result from acetylsalicylic acid medication, are in part due to some systemic disturbance which calcium tends to ameliorate. Either calcium protects by some systemic action, or calcium gluconate reduces the "acid irritation" below a certain minimum necessary for the production of ulcer, or both.

Thus, it follows from our observations and those of Dragstedt and his collaborators that when acetylsalicylic acid, or a salicylate, is given in large doses the optimum protection would be attained by giving both sodium bicarbonate and calcium gluconate. We cannot speak in this regard for other salts of calcium, since we did not use them.

TABLE V

The Effect of Salicylates Upon Gastric Secretion in the Pavlov Pouch Dogs

Drug	Dog	Volume* for six hours			Total acid* (norm. HCl [illegible]) for six hours		
		Std.	Drug	% Change	Std.	Drug	% Change
Acetylsalicylic acid	1	59.3	85.0	+43.3	272.1	374.1	+37.5
	2	99.5	128.0	+28.6	468.0	570.5	+21.8
	3	28.5	57.7	+102.4	101.0	216.9	+114.7
	Av.			+58.1			+57.9
Acetylsalicylic acid and calcium gluconate	1	64.8	56.8	—12.3	272.0	254.2	—6.5
	1	73.0	102.6	+40.4	316.5	450.9	+42.5
	4	47.0	43.9	— 6.5	210.1	192.9	— 8.2
	4	37.9	41.4	+17.1	161.9	183.7	+13.4
	5	117.4	209.1	+78.1	568.1	570.4	+ 0.4
	Av.			+23.3			+24.7
Acetylsalicylic acid and $NaHCO_3$	1	74.0	42.3	—42.8	340.7	210.5	—38.2
	1	58.3	53.1	— 8.9	252.9	275.9	+17.4
	5	181.8	235.8	+27.5	994.6	1150.0	+51.1
	6	99.2	55.2	—44.3	467.8	277.0	—40.8
	Av.			—17.1			—17.2

*Averages of daily determinations for about three weeks. Figures indicate total volume and acidity of gastric secretion for six hours following meal.

CONCLUSIONS

1. In some normal human subjects and normal dogs, single oral doses (1-2 gms.) of acetylsalicylic acid caused gastric retention; the addition of calcium gluconate tended to increase the degree of retention while the addition of sodium bicarbonate increased the rate of gastric evacuation.

2. In normal human subjects and normal dogs, single oral doses of acetylsalicylic acid increased the total titrable acidity of the stomach contents; the addition of calcium gluconate diminished the rise in the acidity, while the addition of sodium bicarbonate decreased the acidity of the contents below that of the controls.

3. In dogs with pouches of the entire stomach, the local application of acetylsalicylic acid caused a definite increase in the neutral chloride, or diluting secretion of the stomach, the addition of calcium gluconate resulted in only a slight increase in the diluting secretion, while the addition of sodium bicarbonate to the acetylsalicylic acid also resulted in only a slight in-

crease in the diluting secretion. None of the solutions increased the formation of HCl significantly.

4. Prolonged daily administration of acetylsalicylic acid to normal dogs to dogs with Pavlov stomach pouches resulted in definite augmentation of gastric secretion. With the addition of calcium gluconate the increase was not nearly so marked, while sodium bicarbonate and acetylsalicylic acid actually caused a decrease in the gastric secretion below the control values.

5. The neutralizing and "inhibiting" actions of sodium bicarbonate and calcium gluconate on the titrable acidity of the gastric contents, and on the output of hydrochloric acid under the conditions of our experiment may play a definite role in the ameliorating effects of these substances upon the degree of gastric irritation and the incidence of ulceration produced by the prolonged oral administration of acetylsalicylic acid to dogs. Whereas the protective action of sodium bicarbonate may be adequately explained by a reduction of acid irritation, this is not true of calcium gluconate, whose protective action against digestive disturbances appears to be due also in part to some systemic action of calcium.

6. From the evidence available it would appear that to obtain optimal protection when giving salicylates in large doses, the salicylates should be administered with sodium bicarbonate and calcium gluconate.

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SECTION VI—*Abdominal Surgery*

Problems in Obstructive Jaundice Cases

By

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RESPONSIBILITY for the preparation of obstructive jaundice patients for operation should be jointly shared by (a) the department of blood chemistry, (b) the internist and his staff, and (c) the anesthetist and the operating surgeon.

Hemorrhage should be given first consideration since over 50 per cent of the fatal cases are due to this factor.

Smith (1) was the first to demonstrate the seriousness of this complication, although, there had been previous reference to it.

Some of the early investigators who believed that the circulation in the blood of an excess bile pigment was responsible for the hemorrhagic tendency were Morawitz and Bierich (2), King and Stewart (3), King, Bigelow and Pearce (4). Morawitz and Bierich (2) believed that bile acids caused this condition.

The work of Brakefield and Schmidt (5), and of Snell, Greene and Rowntree (6) has made it evident that neither the bile pigments nor the bile acids, *per se*, are responsible for the hemorrhages encountered in these cases.

Wright (7) was the first to suggest the use of calcium in hemorrhagic patients. Mayo Robson (8) proposed its use to terminate the bleeding in obstructive jaundice. Schmerz and Wischo (9) discovered that the intravenous injection of calcium lactate into normal human beings shortened the coagulation time of the blood. Kirk, King and Emerson are included among those who made further investigations which revealed that the calcium content was only moderately reduced in the blood serum of icteric patients.

Kerr, Hurwitz and Whipple (10) produced necrosis of the liver in dogs by the subcutaneous injection of phosphorus. They discovered that the blood of the animals would not clot.

It is well known that the main source of fibrinoglobin is the liver. This fact was mentioned by Foster and Whipple (11). The liver is also intimately associated with the production of hemoglobin, according to Whipple.

This brings up the question as to whether there is a substance present, in the damaged liver, which inhibits or delays the clotting.

Since it has been concluded that the hemorrhagic tendency in obstructive jaundice is not caused by the accumulation of bile pigments or bile acids in the blood, and Snell and Greene (12), of our hospital staff (formerly associated with the Mayo Foundation), have demonstrated the following facts to be true: (a) that there is no correlation between either the total or the diffusible content of the calcium of the serum, and (b)

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neither the serum bilirubin nor the delay in the coagulation of the blood in the presence of jaundice, one may infer that some disturbance of the blood calcium may exist in obstructive jaundice, but that its relationship to hemorrhage is rather indirect and is still unknown.

The relationship of fibrinogen to bleeding must also be considered. It has already been noted that the liver is the potent source of fibrinogen; this was confirmed by Whipple and Foster (11). Some observers are convinced that bleeding may be due to a lack of fibrinogen in obstructive jaundice. Moss (13) concluded that the hemorrhagic tendency in these cases was not associated with a deficiency of fibrinogen in the plasma, but that there really was an increase in fibrinogen in a ratio to the changes in the liver condition.

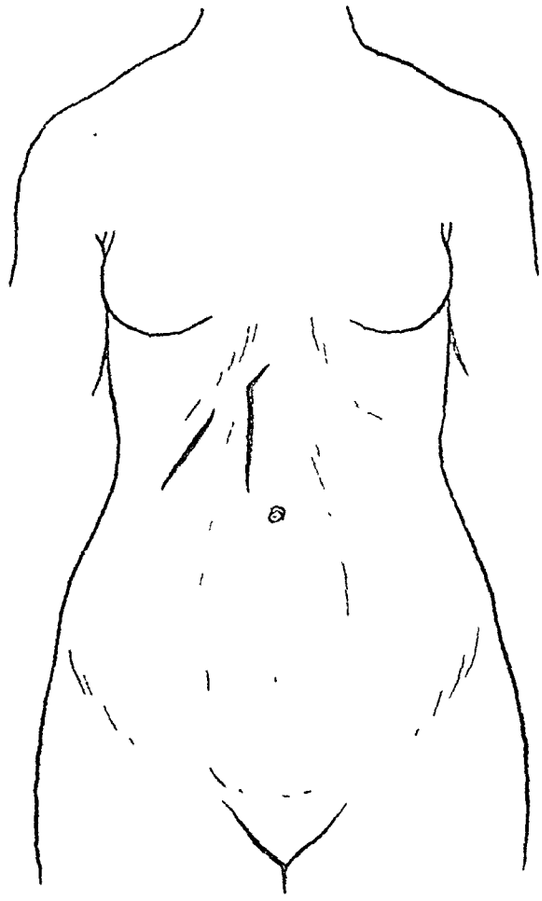


Fig. 1. Primary Incision.

Clinical obstructive jaundice patients have a visible discoloration of the skin, mucous membranes and sclera. Chemically, they have a retention and accumulation of bilirubin in the blood serum. The normal content, circulating in the blood, varies from one part of bilirubin to from 400,000 to 600,000 parts of blood serum. When the concentration reaches from 1 to 40,000, the skin becomes tinged and clinical jaundice appears. Icteric index is the measure of intensity of color of the blood serum as compared with a standard. The normal icteric index varies from 3 to 6. The clinical evidences of jaundice are usually obtained when it reaches 20 or more. Between 6 and 20 is the latent period. Kupffer's cells in the liver and the reticular cells of the spleen are concerned in the breaking down of the hemoglobin into bilirubin. Jaundice arises from the obstruction of the outlet of the bile capillaries after the changed bilirubin has passed through the polygonal cells of the liver plus the bile salts and consequent obstruction and absorption. Obstructive hepatic jaundice presupposes a normal bile formation and a normal mechanical excretion through the apparently normal liver cells. This mechanism does not continue for any great length of time after obstruction has occurred, for normal bile is no longer secreted nor are the liver cells intact. In the beginning, the jaundice becomes obstructive due to a mechanical factor. This does not remain long, for as soon as the obstruction raises the hydrostatic pressure of the fluid within the ducts to a degree equal to that of the secretory liver pressure, there must, of necessity, be a cessation of flow or even a reversal of direction of the bile current with a function conductive to intrinsic damage to the liver cells. Bile salts are the specific products of the liver parenchyma. The production of bilirubin, together with bile salts, is a function limited to the liver. No other organ can simultaneously produce these two chemical substances. Along with bilirubin, bile acids are always present in normal blood. With the Szilard method, the bile acids of normal blood vary from 5 to 12 mg. with an average of 7 mg. Katayama, by a modification of this method, failed to find bile acid in normal urine. An abnormally rapid rate of hemolysis elevates the bilirubin of the blood serum, but does not influence the concentration of bile acids. On the other hand, the production of liver damage increases the bile acids; but this has relatively little effect upon the bilirubin of the blood serum. Even in cases of cholecystitis with transient biliary obstruction, there is a very definite increase in bile acids of the blood serum. The concentration of bile acids is also greater in some cases with normal icterus indices than in others with hyperbilirubinemia. Therefore, it is of paramount importance to determine the bile acids in the blood, in addition to bilirubin, since the increase of bile acids is an absolute indicator of liver injury. Urobilinuria is also an index as to the extent of the impairment of liver function. Normally, it does not exceed 30 mg. in 24 hours by the method of Elman and McMaster. However, in obstructive jaundice, urobilin is negative and excreted in minute amounts forming a striking contrast to catarrhal jaundice. On the other hand, in obstructive jaundice, there is an increased elevation of the icterus index disclosing a hyperbilirubinemia. The bile acids are increased above normal but they do not parallel the icterus index. There is also a distinctive change in the chemical composition of the blood in obstructive jaundice as shown by an increase of cholesterol which is present in two forms: (a) free alcohol, and (b) combined with acid as esters. Normal blood contains from 160 to 200 mg. per 100 ml. In obstructive jaundice, it is increased and may even reach 1,000 per 100 ml. The icterus index, in these cases, may go as high as 200, bile acids to 75 mg. per 100 ml., and direct and indirect van den Bergh, four plus.

In making an estimate as to the extent of the impairment of liver function, the determination of nonprotein nitrogen, urea, uric acid, and the amino acid nitrogen, which must be made daily, (preferably in the morning), are essential to an adequate estimation of complete liver function, and for the differentiation of the types of jaundice. Biochemical analyses must include icterus index, bile acids, blood sedimentation test, cholesterol, nonprotein nitrogen, urea and amino

nitrogen, uric acid of the blood, and urobilin excretion in the urine.

Blood sugar determinations are necessary since the carbohydrate metabolism is also disturbed by virtue of the fact that the liver regulates, quantitatively, the amount of carbohydrate that is furnished to the body cells in the varying conditions of carbohydrate intake

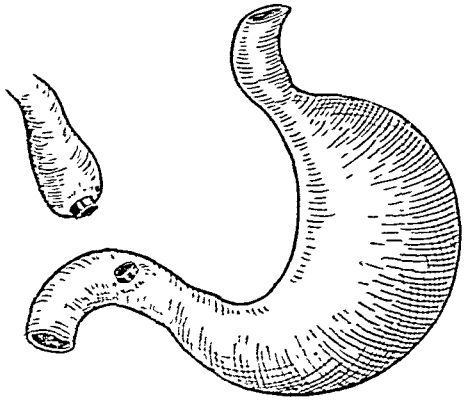


Fig. 2. Insertion of Murphy Button, Anastomosing Gall Bladder and Drainage Tube.

and bodily activity. The internist should order insulin in the suitable cases.

There is a kidney dysfunction in many of these patients. Three distinct procedures should be used to determine renal efficiency. Each of them is based on different principles. The method described by Lashmet and Newburgh (14) is advocated for measuring the concentrating ability of the kidneys. The urea excreting-function should be gauged by the urea clearing test of Van Slyke since it has been generally accepted due to its practical demonstrated worth. The efficiency of dye elimination should be measured by the fifteen-minute phenolsulphonephthalein excretion test because Van Slyke (15) and others have shown that the two-hour phenolsulphonephthalein excretion test measures impairment of kidney function only when extensive renal damage actually exists. According to Chapman and Halsted (16), the excretion of this dye, during the first fifteen minutes following its injection, is decidedly a more sensitive test which is really comparable with the urea clearance as a measure of renal efficiency.

Mosenthal and Bruger (17) recently reported that the "urea ratio" (the percentage of the nonprotein nitrogen which is urea nitrogen, *i. e.*, $\frac{\text{nonprotein nitrogen}}{100 \times \text{urea nitrogen}}$) is a satisfactory index of renal efficiency. They believe that the urea ratio is a correct indication of kidney function despite the fact that the concentration of both urea and nonprotein nitrogen are within normal limits in the blood. Their method is most acceptable since there is an excellent agreement between the urea ratio and the urea clearance.

Since over fifty per cent of the fatal issues are due to postoperative hemorrhage, the clotting time of the blood is a very essential test. In many of these icteric patients, there is a hypochlorhydria, as is evidenced by the blood determination of the chlorides. Inflammatory infiltration about the ducts and even about the finer channels within the hepatic lobule, along with exfoliated epithelium and thrombic formation within the ducts, themselves, are further evidences of the severe injury to the liver.

The various tests enumerated above, together with the routine physical examination, including Wassermann test, blood count, especially Schilling, cardiogram and roentgenogram, impress one with the seriousness of the problem in these patients and also the importance of group consultations, particularly, as to the advisability of operative procedure. In the long-standing, toxic jaundice patients, surgeons are entitled to a helpful sympathy since the operative mortality rate is high.

One of the most important functions of the liver is the protection of the body against poisonous substances which are formed in the intestines. The fact has been established also that much of the power of the liver to carry out this detoxicating function depends upon its glycogen content. As early as 1892, Roger (18) recognized the detoxicating action of the liver. The experiments of Graham (19) and of Opie and Alford (20) should convince one of the extreme importance of the introduction of glucose or dextrose solutions.

For some time, investigators have been convinced that the liver produced an anticoagulant in patients with jaundice. The majority of them have professed ignorance concerning the exact cause of hemorrhagic tendencies in this disease.

When proper consideration for the preparation of these icteric subjects is made, the amount of dextrose or glucose solutions to be administered should not be estimated in centimeters but in quantities of liters or gallons. For many years, it has been generally known that the intravenous injection of 5% solution of dextrose or glucose does not produce any harmful effects upon the vein. General preference is usually given to the Hendon, Tauroff or Lindeman needles to be used for the injection. Large amounts of the 10% solution may be administered by utilizing the Murphy drip. The 5% solution is generally injected under the skin. Ampules of a 25 to 50% solution of glucose in 50 to 100 c.c. quantities should ke kept in reserve for emergencies. A high caloric diet, supplemented with highly sweetened fruit juices, is recommended for the patient's nourishment. Having properly classified the type of the patient's blood, two or three donors should be held available, pending the possible need for massive blood transfusions. It is well to bear in mind that 65% of the body weight is composed of water. Consequently, a patient weighing 100 Kg. has a total water estimation of 65 Kg. or 6500 centimeters. A 10% loss in water may prove fatal to the patient.

Judd, Snell and Hoerner (21) were the first to present an apparently reasonable explanation regarding the increase in coagulability of the blood in jaundiced patients by the use of blood transfusion. They have shown that anoxemia was present in some instances of jaundice. In the presence of a serious liver condition, anoxemia predisposes a hemorrhagic tendency. These three investigators state that there are two types of this affection: *viz.*, anoxic anoxia and anemic anoxia. The first can be corrected by placing the patient in an oxygen tent, and the second by blood transfusion. They suggest that the hemoglobin is changed in these

cases and that oxygen is not omitted in a like amount as in normal or transfused blood.

At the present time, some investigators may become intrigued with the idea of carrying on experiments to obtain a liver extract, produced from the parenchyma of the organ, in order to determine whether this fluid will help to counteract the anticoagulating substance

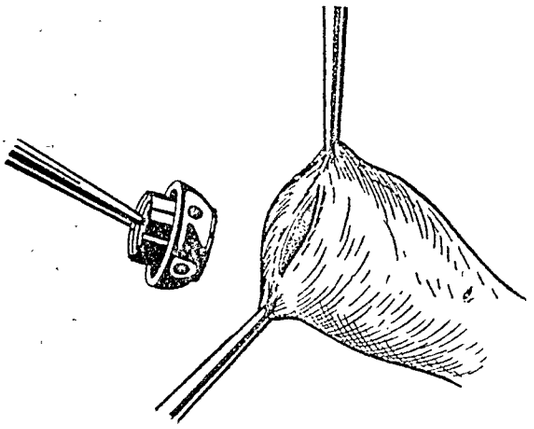


Fig. 3. Secondary Incision.

developed in the injured, diseased, or toxic livers existing in cases of obstructive jaundice.

In presenting this article, it has been the aim of the author to appeal to laboratory workers, sufficiently interested in this condition, to attempt to produce some extract or serum that will help combat this anticoagulating process of the diseased liver.

OPERATIVE CONSIDERATIONS

Without exception, all operative procedures should be performed in two stages. The first is to institute drainage of the gall bladder when the obstruction is below the entrance of the cystic duct which is true in about 90 per cent of instances. This is accomplished by using a modification of the Kocher or Courvoisier incisions, making it more longitudinal, as in Fig. 1. After a thorough exploration of the common duct and having determined the point of obstruction, the gall bladder fundus is then brought up to the aperture of the abdominal incision. Following sufficient packing and walling off, this viscus is drained with a trocar and cannula connected with a rubber tube; the edges of the aperture are held taut with Allis clamps. The female portion of a small size Murphy button is next introduced into the opening of the gall bladder. The male end of the button is inserted into one end of a long rubber drainage tube. The corresponding parts of the Murphy button are then snapped together. In this way, intermittent drainage is instituted and only small quantities are permitted to drain away since one of the most serious factors, at this operative stage, is the danger of a sudden release of suppressed bile which would result in a decrease of the pressure in the common duct. This, in turn, would accelerate the reduced flow of portal blood in the liver and would wash out the toxic substances from the damaged organ into the general circulation. There are several advantages in using the Murphy button, *viz.*, the absolute hemostasis of the edges around the opening of the gall bladder, its quick disconnection, and a further important function to be performed in the secondary stage of the operation. Some surgeons prefer a 28 or 30 F. Pezzer catheter. Following the drainage, performed under local anesthesia, a chemical analyses of the material obtained and a further check-up in the blood and urine chemistry is regularly made. The improvement evidenced by some of these cases after a 72 hour drainage may be amazing.

The consultants having agreed upon the time for the second stage of operation, the operating surgeon proceeds to make a Mayo-Robson or Mayo incision. Spinal anesthesia may be administered, providing the condition of the patient warrants it. However, the Author advises the use of a more modified anesthetic, such as cyclopropane, ethylene combined with a local anesthesia, or avertin, in small amounts may be used as a preliminary anesthetic. The Mayo-Robson incision is closer to the median line than the first one. If the operator discovers that he is dealing with a malignancy of the pancreas, he should disconnect the gall bladder fundus, containing the Murphy button, and use the other end of the button that was inserted in the drainage tube. After proper sterilization, the neighboring first portion of the duodenum or stomach should be incised and this part of the Murphy sutured in and the two parts connected. Drains should then be inserted down to Morrison's pouch and also to the Murphy button anastomosis.

If the obstruction consists of a large impacted stone situated in the lower portion of the common duct, as is so often the case, this area should be dealt with by reflecting and retracting the second portion of the duodenum having, first, incised the peritoneum on the right side. This approach is quite simple and easy as compared with McBurney's transduodenal technic. A T-shaped tube is then inserted. The gall bladder is not to be disturbed since there is an actual or potential pancreatitis to counteract and the gall bladder drainage is most essential in this complication.

After exploring the cause of the obstruction, if a complete stenosis of the lower part of the common duct is found with repair of this organ out of the question, the proximal stump must be used and the end is then

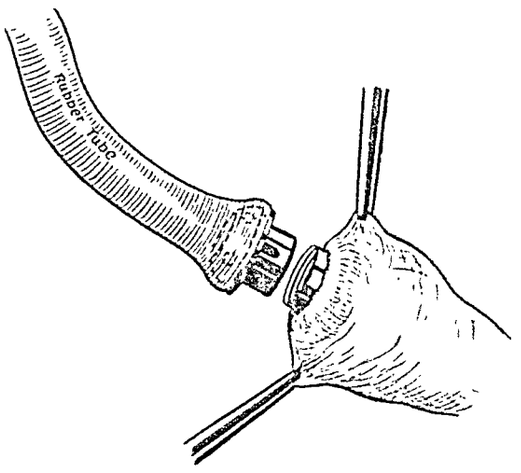


Fig. 4. Anastomosing Gall Bladder and Pylorus with the Murphy Button.

inserted into the proximal duodenum. If the end, to be inserted, is split into four parts, using longitudinal incisions of half a centimeter, each of these parts can be sutured to the duodenal wall, following their insertion, by first threading a nontraumatic suture through the edge before its introduction into the proximal duodenum. Greater security is given, along with

the bile current, by keeping the edges open so that no stenosis can occur.

A direct anastomosis should be used in cases of common duct stenosis even when there exists a virtual destruction. It is made possible by hooking a dull retractor, shaped like an aneurysm needle, over the V-shaped juncture of the hepatic ducts to steady the anastomosis. This is especially true in thin subjects where it is comparatively easy to repair the tissues even though a small portion of the common duct is left with which to make an anastomosis between the duodenum and the common duct.

Unless otherwise unavoidable, the Author wishes to emphasize that the old, obsolete technic, exemplified by the Sullivan tube method, in which a space is left filled in by a rubber tube and covered over by various methods, should not be used. From personal observation, the writer has found that very few operations of this kind have been successful since the stenosis becomes more acute and the adhesions aggravate the extreme seriousness of further exploratory dissection. Therefore, a direct anastomosis of at least a part of the cut edges of the common duct is essential. Failing to accomplish this, an anastomosis of even a small stump of the upper portion of the common duct to the duodenum should be made. On the cadaver in thin subjects, it offers no great difficulty.

CONCLUSIONS

To improve coagulation, transfusions of whole blood and glucose solutions should be administered. At the present time, the extreme value of these solutions in this complication is more fully appreciated, a fact which was unknown a few years ago. The Author has entirely discontinued the calcium solutions which he formerly used to decrease the clotting time, since massive blood transfusions have wholly supplanted the older methods. Ten per cent calcium chloride solutions and ampules of calcium gluconate are useful in order to increase the blood calcium only to the extent of calcium deficiency. Chloride deficiency is improved by the introduction of normal saline and diluted hydrochloric acid solutions by mouth. One dram should be given daily in divided doses, gradually increasing the amount, hypertonic solutions should be introduced intravenously if a serious chloride deficiency exists. The administration of insulin should be made in patients who show increased blood sugar. The diet consists of various fruit juices and cereals, unless contradicted by some special complication.

These patients suffer a fall in body temperature during the course of the operative procedures. This condition must be counteracted by the use of hot laparotomy pads, short exposures, and a warm operating room.

The loss of fluids, brought about by the drainage, must be counter-balanced by the introduction of a glucose or dextrose solution. The drainage may be clamped for a certain length of time during the course of each hour. The Author wishes to reiterate the extreme caution that should be exercised, when drainage is instituted, to regulate the escape of bile to small amounts.

The time-factor is one of the most serious considerations because, at best, these icteric patients are poor surgical risks. It is necessary to make a thorough check-up in order to ascertain that the drainage tubes, Murphy buttons and syringes are in perfect condition prior to operation. This may appear strange to the uninitiated, but the Murphy buttons fit only in pairs and drainage tubes have been known to have had a lumen that was imperfect.

There appears to be little or no excuse for the delay in sending these patients to a hospital for proper diagnosis and preoperative treatment. Yet, daily, subjects are admitted in the late stage of jaundice due to obstruction.

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Experimental Peptic Ulcer*

The Effect of Surgical Duodenal Drainage Upon Dogs and the Value of Histidine in Preventing Ulcer

By

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A. G. Weiss and E. Aron, in 1933 (1), reported that daily injections of histidine prevented the formation of peptic ulcers in dogs that had been subjected to the operation of surgical duodenal drainage. Their report contains one series of four animals and another series of two animals treated with histidine and sacrificed three to ten weeks after operation. Of these six dogs only one developed an ulcer and the latter was ascribed to a technical oversight. Inasmuch as many workers (2, 3, 4, 5) have shown that this operation usually yields peptic ulcers in almost 100 per cent of dogs, these findings seemed significant. Weiss and Aron explained their results on the assumption that the ulcers which develop in dogs with physiological exclusion of the duodenum are due to a "general disturbance of metabolism based upon a lack of the indispensable amino-acid, histidine." They also emphasized the loss of weight and anemia which develop in these animals as being manifestations of deficiency. This report led shortly to the widespread use of histidine in the treatment of patients with peptic ulcer. Meanwhile there have been, to our knowledge, no reported attempts to confirm the original experimental findings.

Our own experiments were undertaken for this purpose. It was considered advisable to have a larger series of animals and to allow them to survive for longer periods of time than did Weiss and Aron. During the course of the investigation numerous physiological and pathological changes resulting from surgical duodenal drainage apart from the development of ulcer were found. These findings are reported here in detail because they have not received due emphasis in the literature, even though the administration of histidine had no apparent effect upon them.

EXPERIMENTAL METHODS

Nineteen dogs ranging in weight from 9 to 18 kilograms were subjected to surgical duodenal drainage according to the technique of Mann and Williamson (2) with minor modifications. The duodenum was divided at a point about 1 centimeter beyond the pylorus and the jejunum was divided about 10 centimeters below the ligament of Treitz. The lower end of the resulting isolated loop of bowel was anastomosed (side to side) with the terminal ileum at a distance of 25 to 40 centimeters from the ileocecal valve, after closing both open ends of the loop with purse string sutures. The continuity of the intestinal tract was reestablished by an end to end anastomosis of the jejunum with the short remaining portion of the duodenum adjacent to the pylorus. Fine plain catgut was used for the intestinal anastomoses. No clamps were applied to the gut during the operation.

After operation the dogs received daily saline and glucose infusions and no food or water was given by mouth for four days. The animals were then placed on the regular diet of the Animal Care Department which includes meat scraps and bones, vegetables, rice, bread and milk. The dogs were permitted to survive until moribund or until death occurred unexpectedly. Routine autopsies were done on all animals including microscopic study of the thoracic and abdominal organs of most of them.

Blood chemistry studies were done on some animals before operation and at intervals after operation. All blood samples were obtained 24 hours after feeding and at least four hours after food pans had been withdrawn. Total blood amino nitrogen was determined by the Folin colorimetric technique using a glycine standard. The methods for the other blood determinations were those used by Atchley, Loeb and Benedict (6, 7) in work previously reported from this department.

Tissue analysis for amino nitrogen content was made by means of an adaptation of the method of Folin for blood amino nitrogen. Small portions of the stomach and proximal jejunum were removed within one to two minutes after the animal was sacrificed and dropped into approximately 10 centimeters of distilled water at a temperature of 90° C. to stop autolysis. The tissues were then weighed while moist and ground finely with sand. The volume of the mixture after grinding was brought up to 60 c.c. by the addition of water, 6 centimeters of 10 per cent sodium tungstate and 6 centimeters of two-thirds normal sulphuric acid. After shaking, the mixture was filtered. The determination of amino nitrogen was then made according to the Folin technique using 3 to 5 centimeters of the filtrate for the unknown and comparing against a standard containing 0.07 mg. of glycine. The final mathematical calculation was made as follows:

$$\frac{60 \times .07}{\text{c.c. of filtrate} \times \text{weight of tissue} \times 2} \times \frac{U}{S}$$

In some animals, gastric secretion was studied before and after operation. For this purpose a broth meal was used which was given by stomach tube. This procedure was adopted for fear that some animals might refuse to eat a test meal voluntarily when cachexia developed, and also because the normal acid response to broth is slight and any increment in acidity after operation could be easily detected. The meal consisted of 200 c.c. of 1 per cent Liebig's beef extract. Gastric contents were withdrawn either 30 minutes or one hour after the meal was given and the concentrations of free and total acid were determined by titration with N/100 sodium hydroxide using Toepfer's solution and phenophthalein as indicators.

RESULTS

Effect of Histidine upon the Development of Jejunal Ulcers: Surgical duodenal drainage was performed upon 19 dogs, 17 of which survived the immediate

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post-operative period. In order to determine whether injections of histidine would protect against the formation of ulcers the animals were divided into two groups. Group I, consisting of five dogs, was a control group to which no histidine was given and in which jejunal ulcers could be expected to develop. Group II, composed of 12 dogs, received l-histidine monohydrochloride made up in a 4 per cent solution in distilled water and administered intramuscularly once a day immediately before the animals were fed.

of the first portion of the jejunum not involving the muscular coat. The latter animal had died accidently of acute intestinal obstruction. Eliminating this animal which might have developed a true ulcer of the jejunum if it had survived for a longer period, five out of eleven, or 45 per cent of the dogs which received histidine failed to develop ulcers in contrast with the control group in which all had ulcers. There was no correlation between the size of the dose of histidine and the formation or absence of jejunal ulcer.

TABLE I

Results of histidine administration to dogs with surgical duodenal drainage. Dogs No. 1 to 5 received no histidine. Dogs No. 6 to 17 received daily injections of histidine

Dog No.	Pre-op. weight kg.	Per cent of body weight lost after operation	Post-op. duration of life	Mgs. of histidine—HCl per kg. of initial weight	Result
1	13.9	48	63 days	None	Three jejunal ulcers with one perforation. Peritonitis.
2	17.1	49	51 days	None	Three jejunal ulcers with one perforation. Peritonitis.
3	10.0	47	63 days	None	Perforated jejunal ulcer. Several erosions in antrum. Peritonitis.
4	9.0	40	63 days	None	Three jejunal ulcers. One walled off perforation.
5	10.9	44	104 days	None	One shallow jejunal ulcer.
6	11.0	39	59 days	7.3	No ulcer or erosions.
7	13.8	47	75 days	5.8	No ulcer or erosions.
8	11.0	52	55 days	7.3	No ulcer or erosions.
9	16.8	44	94 days	4.8	Single indurated ulcer just distal to gastrojejunal anastomosis.
10	9.0	33	87 days	8.8	Small perforated jejunal ulcer.
11	13.2	37	41 days	7.6	Large single jejunal ulcer.
12	9.0	31	31 days	8.8	Single jejunal ulcer.
13	11.9	42	40 days	6.8	No ulcer or erosions.
14	17.5	42	56 days	6.9	Small superficial erosion in jejunum.
15	11.8	43	49 days	6.7	Multiple ulcers in jejunum.
16	11.0	47	82 days	10.9	No ulcer or erosions.
17	13.5	34	57 days	8.9	Large perforated ulcer in jejunum.

The dosage was varied for different animals as shown in Table I, ranging between 4.8 and 10.9 mg. per kilogram of the body weight before operation.

Group I: The five control animals survived 51 to 104 days after operation. Three of them died of general peritonitis due to perforated jejunal ulcers. The other two were sacrificed when moribund and found to have jejunal ulcers which in one dog had perforated and been walled off by adhesions. The ulcers were multiple in three of the animals and solitary in the other two and all were located in the first portion of the jejunum a few mm. beyond the line of anastomosis with the stomach.

Group II: The 12 dogs which received daily injections of histidine survived for 31 to 94 days. Three died of cachexia, one of hemorrhage from a jejunal ulcer; one died of acute intestinal obstruction due to a peritoneal band on the 56th day and seven were chloroformed when moribund. Six of the 12 dogs showed jejunal ulcers which in two instances had perforated and been walled off by adhesions. In one of these six the ulcers were multiple and the other five had solitary ulcers of the jejunum. Of the remaining six animals in the group, five were found to have no ulcers or erosions and one had only a small superficial erosion

CLINICAL PICTURE IN SURGICAL DUODENAL DRAINAGE

The course after operation was characterized by a gradual almost continuous loss of weight and strength and was the same in both groups of animals. The duration of life ranged between 31 and 104 days, averaging about two months. Loss of weight occurred in spite of a fairly normal appetite, the dogs usually eating well throughout the post-operative course, except for the last several days of life when they usually were too weak to stand up and eat. The total loss of body weight in the entire group at death varied between 31 and 52 per cent of the initial weight.

Watery diarrhea was noted frequently during the first two weeks after operation but was uncommon during the remainder of the course. Tarry stools also did not occur after the first few post-operative days until late in the picture. Stool guaiac determinations were done at intervals in an effort to detect the presence of ulcer but were frequently negative in animals which were demonstrated to have ulcers shortly afterward. Stools were also stained for neutral fat and fatty acid crystals but no increase in the amount of unabsorbed fat was found except on one occasion.

As time progressed the buccal mucosa became very pale. In a few instances ulcerative stomatitis developed terminally. A striking feature which was usually noted within a few weeks after operation was weakness of the extremities, more particularly of the hind quarters. Death finally occurred, usually as a result of cachexia or perforated ulcer.

CHANGES IN BLOOD CHEMISTRY

A number of important changes were found in blood chemistry after surgical duodenal drainage had been performed. No differences, however, were revealed between the group which received histidine and that which did not.

Determinations of the total serum electrolyte pattern were done on two dogs approximately two months after operation. The results are given in Table II. One animal (No. 4) was a control and was sacrificed on the day that these determinations were done and shown to have a perforated ulcer of the jejunum walled off by adhesions. The other dog (No. 14) had received daily injections of histidine. This animal died of acute intestinal obstruction five days after the blood studies were done and had a small superficial erosion of the first portion of the jejunum. Symptoms of the acute obstruction did not become apparent until about 12 hours before death.

A change in the distribution of the anions had occurred in both of these animals. Comparison of the findings with the normal figures for dogs, published by Atchley and Benedict (6) shows that a marked decrease in serum protein and bicarbonate content had occurred. This change had been compensated for by an increase in serum chloride. The values for total acid and total base fell within the lower limits of normal. The distribution of sodium and potassium was within normal limits but the calcium was somewhat low in one animal. Total base was estimated by adding two milli-equivalents for undetermined magnesium. Calculation gives normal values for undetermined anions (sulphate and organic acid). The total serum cholesterol was also determined on the same animals and found to be rather low in both of them.

The fall in serum protein was followed at intervals in a number of animals (see Table III). The values obtained before operation varied between 5.1 and 6.6 grams per cent. A fall was detected shortly after operation and continued gradually and progressively throughout the course. Terminal values were obtained within two weeks of death in four dogs (excluding dog No. 14 which died accidentally) and varied between 3.4 and 3.7 grams per cent.

Partitions of serum protein were done on three occasions shortly before death of the animal. The figures obtained were as follows:

Dog No.	*Day*	*Albumin*	*Globulin*
4	63	1.7	1.7
14	51	1.9	2.3
5	78	2.6	1.5

These figures show that the decrease in serum protein had occurred in both the albumin and globulin fractions although it was greater in the albumin fraction.

Total blood amino nitrogen was studied before operation in six dogs and after operation in ten dogs. Repeated determinations shown in Table III on animals No. 4 and No. 5 before operation revealed wide fluctuations in the normal "fasting" values in the same animal. The range of normal values occurring in 12 observations on these and four other dogs extended from 8.7 to 13.7 mgs. per cent of amino nitrogen. Twenty-seven determinations were made on 10 dogs at various intervals after operation, with results varying between 6.7 and 11.3 mgs. per cent. The fluctuations found in individual animals were of the same degree as before operation and no consistent downward trend was observed. It was of interest, however, that in eight of the ten dogs, the blood amino nitrogen fell below the lowest ante-operative value of 8.7 mgs. per cent at some time during the post-operative period. No difference was found between the values obtained in the control animals and in the animals receiving histidine injections.

TABLE II

Serum Electrolyte Partition After Operation of Surgical Duodenal Drainage

Control	Non-Protein N mg. per 100 c.c.	Sodium	Potassium	Calcium	Chloride	Bicarbonate	Phosphate	Protein	Total Base	Total Acid	B—A	Cholesterol mg. per 100 c.c.
Dog No. 4 63 days after operation	35	143.8	4.7	3.9	118.7	19.4	2.5	7.9	154.4	148.5	5.9	132
Dog. No. 14 51 days after operation (received histidine)	20	143.7	5.0	4.7	121.5	15.5	2.5	9.8	155.4	149.3	6.1	120

All figures except serum cholesterol and N. P. N. are expressed in milliequivalents per liter. The total base is calculated by assuming two milliequivalents for the undetermined blood magnesium

HYDROCHLORIC ACID SECRETION

Twenty-three test meals were done before operation in six dogs and the free acidity was found to vary between 0 and 40. Repeated observations on individual animals gave fluctuating results (see animals No. 4 and No. 5 in Table III). Thirty post-operative determinations were made on eight animals and again variable results were obtained ranging from 0 to 36 degrees of free acidity. It was clear, however, that no tendency to an increase in the concentration of hydrochloric acid in the stomach after a broth meal

TABLE III

Serum protein, total blood amino nitrogen and acid secretion in dogs before and after surgical duodenal drainage. Dogs No. 4 and No. 5 were control animals (see text). Number 18 and 19 died shortly after operation. The remaining animals received histidine.

Dog No.	Serum protein gm. per 100 c.c.		Amino nitrogen mg. per 100 c.c.		Test meal	Free Acid	Total acid
4	Pre-op.	6.6	Pre-op.	9.6	Pre-op. (1 hour)	30	44
	2 days post-op.	6.4		10.5		0	16
	27 days post-op.	5.8		11.4		0	10
	40 days post-op.	4.7	20 days post-op.	11.2		5	26
	54 days post-op.	4.2	27 days post-op.	8.3		12	36
	63 days post-op.	3.4	40 days post-op.	7.4		9	18
			54 days post-op.	7.7		4	23
						18	34
						30	44
						0	16
					12 days post-op. (1 hour)	16	27
					28 days post-op. (1 hour)	19	31
					40 days post-op. (1 hour)	24	44
					49 days post-op. (1 hour)	36	50
					58 days post-op. (1 hour)	26	62
					63 days post-op. (1 hour)	0	26
5	Pre-op.	6.6	Pre-op.	9.5	Pre-op. (½ hour)	32	48
	2 days post-op.	5.9		13.7		40	50
	27 days post-op.	5.2		11.9		12	30
	40 days post-op.	4.7	20 days post-op.	10.4		12	32
	61 days post-op.	4.7	27 days post-op.	9.7		36	52
	78 days post-op.	4.1	40 days post-op.	7.3		30	48
			61 days post-op.	11.3		14	26
			78 days post-op.	8.2	12 days post-op. (½ hour)	32	52
					28 days post-op. (½ hour)	28	52
					40 days post-op. (½ hour)	11	28
					49 days post-op. (½ hour)	24	52
					61 days post-op. (½ hour)	0	37
					96 days post-op. (½ hour)	6	34
10	Pre-op.	5.6	26 days post-op.	8.4	11 days post-op. (1 hour)	8	19
	11 days post-op.	5.6	39 days post-op.	10.3	26 days post-op. (½ hour)	11	22
	39 days post-op.	4.8	55 days post-op.	6.7	41 days post-op. (½ hour)	18	26
	55 days post-op.	4.1	76 days post-op.	8.0	50 days post-op. (½ hour)	16	26
	76 days post-op.	3.7			63 days post-op. (½ hour)	31	54
					78 days post-op. (½ hour)	5	21
11	Pre-op.	5.5	14 days post-op.	8.2	14 days post-op. (1 hour)	18	62
	14 days post-op.	5.6	35 days post-op.	9.8	18 days post-op. (1 hour)	24	46
	35 days post-op.	3.7			35 days post-op. (1 hour)	0	36
12	Pre-op.	5.1	26 days post-op.	7.7	11 days post-op. (1 hour)	0	25
	11 days post-op.	4.9			26 days post-op. (1 hour)	0	32
13			16 days post-op.	8.6			
			36 days post-op.	8.7			
14	45 days post-op.	4.0	28 days post-op.	8.5			
	51 days post-op.	4.2	45 days post-op.	10.5			
15	40 days post-op.	3.6	20 days post-op.	10.9	42 days post-op. (½ hour)	0	34
			38 days post-op.	9.0			
			48 days post-op.	11.7			
16	Pre-op.	5.8	Pre-op.	11.0	Pre-op. (½ hour)	18	36
			19 days post-op.	9.5	12 days post-op.	4	46
			56 days post-op.	8.2	25 days post-op.	16	48
					41 days post-op.	0	36
					74 days post-op.	0	92
17	Pre-op.	6.6	Pre-op.	10.0	Pre-op. (½ hour)	32	48
	19 days post-op.	5.6	19 days post-op.	9.6	13 days post-op. (½ hour)	4	28
			56 days post-op.	9.0	26 days post-op. (½ hour)	35	42
					42 days post-op. (½ hour)	28	52
18	Pre-op.	5.3	Pre-op.	8.8	Pre-op. (½ hour)	36	52
				9.8		18	40
19	Pre-op.	6.0	Pre-op.	8.7	Pre-op. (½ hour)	28	50
				9.1		23	56

was present after the operation. On the contrary, there was a terminal decrease in gastric acidity. The final test meals done within two weeks of death in seven animals gave very low values for free acid. Five were anacid and two were five and six degrees respectively. The fact that the samples were usually contaminated with jejunal contents or with food residue even after 24 hours of starvation in these animals with marked cachexia, deserves mention. No difference between the gastric acidity of animals receiving histidine and controls was apparent.

TISSUE AMINO NITROGEN

In view of the possibility that histidine might exercise a protective effect against jejunal ulcer by some mechanism involving a local increase in tissue amino nitrogen, determinations of the latter were made on a few animals. The amino nitrogen content of the proximal jejunum and antral portion of the stomach was

studied in two normal dogs, two dogs of the group receiving histidine and one of the controls. The results are given in Table IV. No significant differences were present.

DEVELOPMENT OF ANEMIA

Repeated blood counts were done on two controls and five animals receiving histidine. All of the animals developed a progressive secondary anemia. This anemia was as marked in the group which received histidine as in the controls. No important changes were found in the total and differential white blood counts.

TABLE IV

Tissue Content of Amino-Nitrogen (mg./gm. of tissue). Duplicate specimens of the antral portion of the stomach and upper jejunum in five dogs, three of which had undergone surgical doudenal drainage. Dogs No. 11 and 15 received histidine and Dog No. 4 did not

	Stomach I	Stomach II	Jejunum I	Jejunum II
Dog No. 4	0.42	0.35	0.35	0.43
Dog No. 15	0.40	0.32	0.47	0.34
Dog No. 11	0.34	0.33	0.36	0.37
Normal Dog	0.38	0.33	0.35	0.35
Normal Dog	0.34	0.37	0.42	0.45

PATHOLOGICAL FINDINGS

At autopsy there was a marked decrease in the amount of subcutaneous and omental fat. In some instances, the liver appeared fatty. Submucosal hemorrhages were frequently found in the small intestine and to a less extent in the colon. At times the villi of the upper jejunum appeared shrunken and the surface of the intestine had lost its normal velvety appearance. A few superficial erosions of the antral portion of the stomach were present in three animals. Unusual prominence of the rugae of the fundus of the stomach was seen only twice. There were no other gross manifestations of "gastritis." Edema of some of the abdominal organs, particularly of the stomach and intestine was present in two animals. One of them also had marked ascites and slight hydropericardium and hydrothorax. Dependent edema was never observed.

Microscopic: Sections of the ulcers showed loss of mucosa and at least part of the muscularis, the base of the lesion being covered with a polymorphonuclear exudate and fibrin which in the majority of instances overlay a layer of fibrous and granulatous tissue. The vessels in the base of the ulcer were normal except in two specimens where thrombosis with recanalization had occurred. The mucosa adjacent to the ulcers showed edema, and increase in the number of wandering cells present in the stroma. Fibrosis in the wall of the jejunum was never found beyond a short distance from the bed of the ulcer.

The antral and fundic portions of the stomachs were studied for histological evidence of gastritis. No increase in the number of wandering cells was found and collections of lymphocytes in the mucosa was rare. In some instances, there appeared to be an abnormal dilatation of the mouths of the glands in portions of both the fundus and antrum, with papillomatous projections of the mucosal surface, but it was difficult to estimate whether these findings exceeded the limits of normal variation. Goblet cells in the antral mucosa were few in number.

Sections of the jejunum and colon often showed a reduction in the height of the mucosal layer and a slight degree of atrophy of the muscularis. The atrophy of the jejunal mucosa was less marked in some of the dogs which received histidine than in the controls.

The majority of animals had fatty degeneration of the liver. This change involved the entire liver lobule in some dogs and only the central part of the liver lobule in others. Sections of the kidney showed the presence of large vacuoles in the cytoplasm of the convoluted tubules in some of the animals.

No pathological changes were found in the pancreas, spleen, adrenals, heart, thyroid or parathyroid.

DISCUSSION

These experiments demonstrate that surgical duodenal drainage, in addition to causing jejunal ulcer, results in many other profound changes in the animal, including gradual inanition, alteration in the serum electrolyte pattern with a fall in serum protein, some tendency to a decrease in the blood amino nitrogen, late gastric subacidity, secondary anemia and degenerative changes in the liver, kidneys and other organs. The administration of histidine had no effect upon these changes except that the incidence of jejunal ulcers in the dogs which received histidine was rather low, five out of a group of eleven showing no ulceration. Our results are at variance with those of Weiss and Aron who report complete protection against the formation of ulcers by histidine injection. This is probably due to the fact that our dogs were permitted to survive until moribund whereas their animals were sacrificed after shorter periods of time.

Histidine administration did not cause any increase in the amino nitrogen content of the ulcer bearing tissues, *viz.*, the antrum and jejunum nor in the fasting blood amino nitrogen level. Histologically, however, many of the treated dogs showed less atrophy of the jejunal mucosa than did the controls.

The question of the mechanism underlying the blood and other tissue changes in dogs with surgical duodenal drainage arises. Fatty degeneration of the liver and atrophy of portions of the gastro-intestinal tract are known to occur in prolonged starvation (8) and are probably part of the general picture of cachexia in these animals. It is also possible that drainage of duodenal juice into the terminal ileum is associated with a loss of some of the constitutents of these juices due to incomplete reabsorption and that a condition similar to a pancreatic fistula is produced. In these circumstances, the fatty degeneration of the liver might be analogous to that described in dogs with pancreatic fistulae and pancreatectomy (9).

The fall in serum protein in our animals was similar in rate to that found by Weech, Goettsch and Reeves (10) for dogs maintained on a deficient protein diet. It differs, however, in that it usually did not fall low enough to produce edema. Weech (11), furthermore, found that approximately one-fourth of his dogs on a low protein diet develop peptic ulcers. These facts suggest that surgical duodenal drainage may result in incomplete digestion or absorption of protein con-

TABLE V

Dog No.	No. days post-op.	Hgb. %	R. B. C.	W. B. C.	Polys.	Eos.	Bas.	Lym.	Mon.
No. 4	0	104	7.2	12,000	65	7		15	13
	0	90	6.4	12,900	60	6		23	11
	6	84	5.6	18,600	73	5		15	7
	27	78	5.3	18,600	86	2		11	1
	41	78	5.5	21,200	71			21	8
	56	60	4.0	11,200	72			20	8
No. 5	0	100	5.0	11,200	50	28		19	3
	0	106	6.2	13,300	54	21		19	4
	6	91	6.2	19,100	74	6		13	7
	27	95	6.5	23,400	75	4		9	12
	41	75	4.9	8,700	72	6		19	3
	56	73	4.8	6,900	53	2		36	9
	76	76	5.0	13,100	83	2		3	12
	96		4.1		84			8	8
No. 10	0	92	7.5	11,000	75	6		16	3
	10	89	6.5	14,900	67	2		19	12
	28	83	6.5	24,900	81	1		16	2
	57	81	6.1	24,850	79	1		17	3
	72	62	4.3	6,900	72			24	4
No. 11	0	75	5.7	6,000	55	4		32	9
	13	79	6.1	12,400	57	3		27	13
	31	60	4.6	11,400	73	1		10	16
	38	57	4.2	11,000	69		1	14	15
No. 12	0	91	6.1	32,300	57	17		11	15
	9	76	5.1	29,600	60	1		34	6
	28	61	4.6	16,900	73			12	14
No. 16	0	106	7.6	9,200	61	15		13	11
	15	87	6.2	17,200	90			5	5
	54	66	4.2	10,000	89			6	5
	74	54	3.0	5,500	88			6	6

Blood counts on seven animals with the operation of surgical duodenal drainage. Animals No. 4 and No. 5 were controls. The others received histidine. The initial blood count was taken before operation in each instance. All animals developed a secondary anemia.

stituents of the food because of exclusion of the bile and pancreatic juice from the upper gastro-intestinal tract.

The decrease in serum bicarbonate after surgical duodenal drainage may be due to a loss of bicarbonate from the outpouring of duodenal contents into the distal part of the intestinal tract where it may be incompletely reabsorbed. It is interesting that this change takes place without a coincidental fall in total base, suggesting that the cations in the duodenal juice are reabsorbed more readily than the bicarbonate. The rise in serum chloride compensates for the fall in serum protein and bicarbonate.

The tendency to a low serum cholesterol is apparently analogous to the decrease which takes place in prolonged starvation (12). The low values for blood amino nitrogen cannot be accounted for in this way, however, since Van Slyke found no diminution in the blood amino nitrogen of dogs after starvation (12).

The secondary anemia of dogs with surgical duodenal drainage might also be accounted for on the basis of partial inanition or possibly impairment of reabsorption of biliary pigments.

The study of the effect of diversion of duodenal juices by operation on gastric acidity suffers from the same handicap which impedes all study of the secretion of the total stomach when it is open at both ends. The normal range of variation in acid concentration is so wide that marked and fairly constant differences must occur under the conditions of a given experiment in order that their significance shall become manifest. The importance of duodenal regurgitation in the regulation of the level of gastric acidity is a subject of controversy at the present time (13, 14). In our own observations, in which only the chemical phase and not the cephalic phase of gastric secretion was studied by means of a weak broth stimulus, no evidence for rise in gastric acidity after elimination of the duodenal juice was found. McCann (3) also found no increase in gastric acidity in response to a meat meal after this type of operation. In our experiments there appeared to be a decrease in acid concentration in the stomach in the last two weeks of life. This might be interpreted as due in some way to the development of cachexia.

The importance of protein deficiency as a factor in the production of peptic ulcer is demonstrated not only by our findings in animals with surgical duodenal drainage but also in other types of experimentation. For example, Hoelzel and Da Costa (15) and others have produced ulcerations in the stomach of the rat on a low protein diet and Rassers (16) and Weech

have observed peptic ulcers in dogs which were fed on diets characterized by protein deficiency. There is, however, no evidence at present of a deficiency in protein metabolism underlying peptic ulcer in human beings.

CONCLUSIONS

1. Surgical duodenal drainage in addition to producing jejunal ulcers causes many other pathological changes in the dog.

(a) Marked cachexia develops.

(b) Changes in the electrolyte pattern occur, including chiefly a fall in serum protein and serum bicarbonate and a rise in serum chloride.

(c) The blood amino nitrogen is variable but tends to be lower after the operation.

(d) A marked secondary anemia develops.

(e) No increase in gastric acidity in response to a broth meal occurs. A decrease in acidity was found during the last two weeks of life.

2. Six of eleven dogs receiving daily injections of histidine monohydrochloride after surgical duodenal drainage developed ulcers. Five controls not receiving histidine all developed ulcers.

3. The administration of histidine did not influence the other physiological and pathological changes described.

4. The administration of histidine did not affect the amino nitrogen content of the jejunum or antral portion of the stomach.

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SECTION VII—*Surgery of the Lower Colon and Rectum*

The Present Status of Radiation Therapy in Carcinoma of the Anus, Rectum and Sigmoid Colon*

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EXPERIENCE has shown that no single method of treatment is suitable for all cases of cancer involving the anus, rectum and sigmoid colon. Although surgery should be considered first, it behooves us to regard irradiation as an addition to the armamentarium for the eradication of this disease. The recent advance in the therapeutic use of radium and roentgen rays is a convincing proof that this method is of value, especially with the improved technique, increased voltage of present-day installations and better selection of cases.

As is known, the therapeutic activity of radium is due to disintegration of the radium atom, by which are produced a series of different radiations, substances and emanations. It has been shown that normal and pathologic tissues are affected by radioactive substances, although the embryonic or immature cells are less resistant than normal calls (8). By the same token, the squamous epithelium of the anus is more resistant to radiation than is the mucous membrane of the rectum and sigmoid colon.

Irradiation, which combines the use of radium and X-rays, may be employed alone or in conjunction with surgery. In either instance the treatment should be selective, since irradiation is not applicable in all cases. The determining factors, and, of course, the results, will depend upon the physical condition and age of the patient, the size and location of the cancer,

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whether at the anus, low in the rectal ampulla, or in the sigmoid; the grade of malignancy and its radiosensitivity; the structures invaded and extent of metastasis (3).

Opinions differ as to the value of radiation therapy before and after operation. May (17) advocates the use of roentgen rays pre-operatively and post-operatively, and employs them routinely. Larson (14) believes that large, inoperable growths may sometimes be rendered operable by these rays, and Schmieden (21) considers this to be occasionally true even though metastasis to the liver has occurred. Binkley favors the interstitial implantation of radon seeds at the time of or immediately following operation, and external radiation at a later date. Yeomans (23) prefers exposure of roentgen rays through six portals of entry, each being treated three times in periods of 30 minutes each, the course to be repeated in six to twelve weeks. Bowing (7) believes that more aggressive radium treatment, followed, after a lengthy interval, by surgical excision, is the procedure in cases presenting themselves reasonably early. He distributes platinum-filtered needles (1 mg.) evenly throughout small growths for 48 hours, or gold radon seeds. In other cases, he employs "contact treatment": two or three radon tubes strapped side by side with adhesive tape so as to form a plaque. The tubes are introduced through the proctoscope against the growth, the normal bowel wall being packed away with gauze soaked in metaphen. A dosage of 60 to 100 mg. hours per square centimeter of malignant tissue is given. This is repeated daily until the entire lesion has been covered.

Fitzwilliams (9) favors a preliminary colostomy and the intratumoral insertion of radium both through the lower loop of the colostomy opening and through the rectum. Four to six weeks after the colostomy is performed, a narrow sigmoidoscope is introduced into the lower bowel loop until the growth is visualized. He inserts a well-protected tube containing 30 mg. of radium into the growth, which is allowed to remain in place for four to five hours. The following day the growth is approached through the anus, with the same dosage and for the same length of time. After a rest of one day, the entire procedure is repeated. Approximately 500 mg. hours of radiation are given directly into the growth. Three courses similar to this are given at intervals of one month. Quick (20) employs a combination of buried emanation, filtered radium internally and externally, and surgical exposure if necessary. For annular growths, he uses 0.5 mm. platinum tubes arranged end-to-end in a small rubber tube which, in turn, is encased in a larger rectal tube. In this way, he has been able to use 500 mg. hours per tube without danger of reaction. Where the tumor is confined to one portion of the rectal wall, he advocates a bougie of solid rubber with platinum tubes in its grooves. Kelly and Ward (14) advise implantation of radon seeds into the growth through a proctoscope. According to their calculations, 1 mc. of radium emanation is sufficient to destroy 1 c.c. of the tumor tissue. Others vary their treatment according to the type of growth; for example, in cancerous stricture of the rectum, Yeomans (22) inserts tubes in tandem of rubber within the lumen. For papillary growths, Jones (13) distributes needles or emanation tubes throughout the tumor and uses a flat oval applicator containing the radium tubes for large, flat, ulcerating lesions. Interstitial irradiation following surgical approach, as devised by Newman and Coryn (18), has been found unsatisfactory by Gabriel (10), who employed the procedure in a series of 89 cases.

Binkley (5), whose experience has been vast in treating anorectal malignancy, remarks that "besides being used as a palliative means in inoperable cases, radiation therapy is capable of producing clinical cures in properly selected, favorable and operable cases." He suggests three distinct groups of cases in which radiation therapy may be employed advantageously: (a) "Favorable and operable cases in which one may expect a clinical cure by this method alone. The tumor, however, must lend itself to interstitial radiation (4); (b) Operable cases in which pre-operative radiation therapy offers advantages in promoting clinical cures; (c) Advanced cases in which radiation therapy, either alone or combined with colostomy, offers the highest degree of palliation." For the favorable group, the first step is external radiation. He uses approximately 900 roentgens through six portals of entry and a perineal field when the growth is in the lower rectum on alternate days. In some cases he employs a 4 gm. radium pack, 8000 mg. hours at 15 cm. from the skin daily; whereas, in others, both forms of rays are utilized. In this case, the roentgen rays are administered to each part with a dosage of a little below the erythema. The radium rays are then given through two to four portals, with a dosage of about 50,000 mg. hours at each portal. Binkley (1) mentions that external radiation is followed by beneficial results in most cases; bleeding is lessened, ulceration is decreased, the tumor becomes smaller, and the degree of mobility is increased. Improvement in the general condition of the patient, with increase in weight and strength, is frequently noted. As a second step, gold filtered emanation seeds are implanted two weeks after completion of the external radiation, the dosage varying from 10 to 75 mc., according to the size of the tumor.

His technique may be described as follows: A proctoscope of suitable length, with an oblique distal opening, is introduced to the upper level of the growth. Under direct vision, the seeds are inserted into the upper portion of the tumor by means of a fishhook needle. These seeds are placed approximately 1 cm. from each other. The proctoscope is slightly withdrawn, at which point another row of seeds is inserted, which procedure is repeated until the entire growth has been treated with the required number. In the advanced, but still favorable, cases, he finds that a colostomy is often required to relieve the partial obstructions. This is performed either before the external radiation or in the period between it and the interstitial application. If the colostomy is so constructed that the gut between the lower opening and the growth is short and without undue tension (6), a sigmoidoscope may be introduced through the lower loop and seeds inserted directly into the tumor.

Where radical surgery is to be combined with irradiation, Binkley employs external therapy alone in cases where adequate dosage of radon cannot be given or when the growth is situated above the peritoneal reflection. A full erythema dose is given through each of six portals three weeks before operation. He uses external and interstitial irradiation as follows: in

perineal resection, a full erythema dose of external irradiation is given, followed by a colostomy in three weeks. After a lapse of one week, gold seeds are implanted and the resection is performed seven to ten days later. In the one stage abdomino-perineal resection, external radiation is given primarily and followed three weeks later by the interstitial insertion of gold seeds. The operation is performed one to two weeks later.

In the advanced cases, he employs external irradiation in sufficient intensity to restrain the activity of the growth. Here ¾ to 1 erythema dose of high voltage roentgen ray is given through each of six portals, in one or two applications, with treatments daily or on alternate days. It does not damage the skin and may be repeated at one or two month intervals. He remarks (3): "Irradiation usually offers the inoperable patient much greater palliation, without the possibility of an immediate fatality, than that provided by incomplete removals."

So far as trans-peritoneal radiation for growths above the peritoneal reflection is concerned, it should be mentioned that Gordon-Watson (12) obtained discouraging results using this method.

It is generally conceded that epithelioma of the anus responds well to treatment with radium because of its accessibility. Mummery (16), as a matter of fact, prefers it to excision, and remarks: "the results of radium treatment are better than those obtained by operation." Pruitt (19) reports good results in these squamous cell carcinomata by inserting needles containing 1.33 mg. of radium into and around the growth, including the ischiorectal fossa. The needles are left *in situ* four to six days, or until a dose of 2000 to 4000 mg. hours is given. In addition, external radiation is given over the sacrum, perineum and inguinal regions by the application of columbia paste containing the needles. In this way, approximately 9000 mg. hours are administered posteriorly and 7000 mg. hours anteriorly over each inguinal region. Souttar (22) employs a moulded apparatus containing 120 to 160 mg. of radium, and applies it for 15 to 18 days. The inguinal glands on each side receive a similar application. Binkley (2), however, advises external radiation of high voltage roentgen rays and radium rays, to be followed by the interstitial implantation of gold filtered emanation seeds. In some cases irradiation may be combined with surgery, as advocated by Yeomans. Here radon capillaries are inserted into the tumor, followed by radical excision in two to four weeks. In a general way it may be said that anal epitheliomata will respond well to interstitial radiation, combined, in some cases, with external radiation. Gordon-Watson (11) believes that if deep infiltration of the ischiorectal fossa, adjacent tissues, or invasion of the inguinal gland has not occurred, an immediate cure may be anticipated with this method.

From the several procedures described, it is clearly obvious that the surgical approach and the use of radium and X-ray, their dosage, screenage and time of application differ markedly with various workers. Yet, even though certain methods have proved unsatisfactory in many cases, are we justified in condemning the use of irradiation as a therapeutic measure?

During the past several months it has been my privilege to review meticulously the records of 500-odd cases of carcinoma of the anus, rectum and colon, nearly all of which had come to necropsy; tissue sections being made in almost every instance. In this study it was appalling to note that in the vast majority of cases, radical surgery or palliative colostomy having been performed, subsequent irradiation had not been employed; yet, on the autopsy table, recurrence and metastasis to various structures were observed.

Just how much radiation therapy would have inhibited the growth is a matter of conjecture, but it is in our power to realize that these cases were not extended the privilege of what radiation therapy might have accomplished. According to one writer, approximately one-half the patients who are subjected to radical extirpation die of cancer. If such is true, postoperative irradiation should be advocated to prevent recurrence. In view of the fact that some investigators have obtained good and favorable results and, in some cases, cures, should not we, as proctologists, with the aid of the radiologist, give the unfortunate patient the opportunity of benefiting by what science has revealed, even though we be keenly appreciative of its limitations? Certainly the combined use of surgery and irradiation should greatly reduce the high mortality as it exists at the present time.

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Annual Abstracts of Proctologic Literature

(May, 1934-May, 1935) By CLEMENT L. MARTIN, M.D., Chicago, Illinois

The complete bibliography from which these Abstracts were made will be published in full in the Transactions of the American Proctologic Society, 1935.

FISTULA IN ANO

N. D. Smith advises delay in incising the abscess until there is definite fluctuation: "incision is indicated as soon as the abscess points or when there is definite superficial fluctuation." Many may not agree with this view. He states that a common practice, that of inserting gauze-strip packing is painful and of doubtful value; on this there will be more general agreement.

Murdoch saves as much as possible of the external sphincter where the fistulous tract crosses it. "Several years ago I began saving the continuity of considerable sphincter muscle at the site of fistulectomy." "A slight amount of freeing of the bowel wall above is done. It is then possible to place the sphincter upward and stitch the rectal wall downward over it fixing the sphincter against solid tissue in a somewhat higher but nevertheless good functioning position. The final result is a more normal anal contour without as much notched defect, this is sometimes marked after the usual operation."

This technic is applicable to about 40% of his cases, in the others the usual fistulectomy is performed.

Allen & Haskell used a two-stage fistulectomy in 119 of 226 cases. This is extending a sometimes necessary procedure beyond what most proctologists will regard as its indication.

HISTORY

Although the name of Bodenhamer crops up every now and then as one reads the literature of rectal disease few of our generation have more than a vague notion of his character or accomplishments. *Kleiner's* sketch of his life indicates that he was forceful and aggressive but selfish and not over-burdened by a regard for medical ethics, that he was capable, a student, and that his publications helped to advance the study of proctology.

INJURIES

Nightingale had a case of rupture of the sigmoid from compressed air. Unlike most of the cases, the nozzle of the air hose was not brought in contact with the anus by a practical joker. The workman was using the air to clean his clothes and accidentally touched the anus. There were several tears of bowel wall too, but none through the serosa. Recovery followed laparotomy and repair of the bowel.

Black & Weisman in 1926 reported 27 cases, 19 of them fatal.

La Croix & Ryan cite the case of a farmer who suffered a common cause of rectal injury—that of impalement. This man slid down a load of hay causing the pitchfork handle, about 2 inches in diameter, to enter and lacerate the anus, rectum and sigmoid. The handle entered the bowel to a distance of 14 inches. He removed it himself. At operation a 6 inch rent in the sigmoid was found, most of the tear being in the mucosa, a relatively small portion through the serosa; a 3 inch laceration in the mesocolon was present. Recovery followed.

Epstein attended at the Lincoln Hospital a man who had inserted two apples in the rectum and who had at various times previously used a cucumber and parsnip in the same manner. On entry the patient had a 2" tear in the recto-sigmoid, localized peritonitis, and free soapsuds in the abdomen. Trauma from efforts at removal and a soapsuds enema explained these. The tear in the recto-sigmoid was not seen proctoscopically although the instrument was passed beyond its site. The star shaped appearance at the center of the apple, as seen in the roentgenogram, was a point of interest. The patient recovered.

INFLAMMATIONS

Several articles reveal the importance of the colon and rectum as foci infection. *Hirschmann's* discussion of the subject is definitely informative.

An unusual type of chronic buccal and peri-anal ulceration is described by *Wiseman* in which diagnosis was impossible and therapy of little avail. *Preusser* emphasizes the importance of anal infection in an article treating of the general phases of the subject.

INSTRUMENTS

Bacon has devised a self-retaining illuminated proctoscope that is a short instrument tapering from the base to an expanded portion at the end, this expanded portion being grasped by the sphincter holds the instrument in place. It can also be used with a light adaptor, thus making it more generally available. He has also devised a stricturoscope consisting of a set of five tubes varying in calibre from ½" to ⅛". By means of these the stricture can be calibrated, dilated, or treated before medicaments are applied. It is illuminated and has an adjustable lens which may be swung into place as desired.

INTRAPERITONEAL VACCINATION

Steinberg & Goldblatt (see 1934 Transactions) found that the injection of heat-killed *B. coli* suspended in a saline solution and injected into the abdominal cavity, decreased the incidence of peritonitis after operation.

Hermann determined that a mixture of streptococci and *B. coli* was more effective than *B. coli* alone.

The former investigators advocate the use of a single intraperitoneal injection of 30 c.c. of 1% gum tragacanth in normal saline solution containing about 200 million heat-killed *B. coli* per cubic centimeter. (Coli-bactragen).

Following Hermann's and Steinberg's work, the use of a vaccine containing both *B. coli* and streptococci was started 8 years ago at the Mayo Clinic and a marked reduction in mortality reported from its use by Rankin and Bargen. This group continues its pre-operative use in colon cases. Some unfavorable reactions following its use have been reported. (See 1934 Transactions, Intraperitoneal Vaccination, Jones' discussion).

Potter's and Coller's experience has been favorable with Coli-bactragen (Steinberg) in 79 cases.

Gundel & Suessbrich have treated 240 cases of peritonitis with "peritoneal serum" and have studied the cases bacteriologically. They used a polyvalent serum containing colon bacillus, gas-gangrene bacillus, and enterococci. They state that of 51 patients given this serum for prophylaxis or treatment, 6 died but 5 of these had heart or lung complications.

Young & Marks have used amniotic fluid concentrate in a series of 48 cases of colon resection with a mortality of only 2% in the whole group. They regard the beneficial effects of vaccines to be non-specific. A preparation of amniotic fluid is now on the market; it is named Amfetin.

SECTION VIII—*Editorial*

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastroenterological Association is in no way responsible for editorial expressions.

WHAT IS AN "INTRACTABLE" PEPTIC ULCER?

FOR several years the medical profession in general has been bombarded with literature about the treatment of "intractable peptic ulcer." The pharmaceutical houses have awakened to the fact that peptic ulcer is a common disease and that there is money in advertising drugs offered as a "cure" for it. Pressure has been brought to bear on research workers in universities to produce some specific substance which would cure an ulcer, so that the substance could be patented and could become a source of income for the university comparable with insulin and vitamin D.

General practitioners, and unfortunately many specialists also, feeling the pinch of the depression, have welcomed the opportunity of giving intravenous treatment twice a week or more, thus adding materially to their incomes, and others, apparently with similar intentions, have devised new methods of treatment requiring either continuous bed or hospital care or frequent office visits. And some surgeons (or let us rather call the type I am referring to, "operators") who had begun to see that operations for simple ulcer were being frowned upon as unnecessary, have seized upon the term "intractable ulcer" as an excuse for the performance of new, more radical operations in greater numbers. We hardly ever see an ulcer patient today who has not been through one or more of these newer tortures.

Now what is this bugaboo "intractable ulcer," that has so suddenly been raised to frighten medical practitioners? Feeling that perhaps our unfamiliarity with the subject might be due to our seeing only "easy" cases in private work, and realizing that the more severe and previously neglected cases would be found in the hospital, we have been asking our internes if they could tell us how many "intractable" cases they have seen. They have looked puzzled and have asked us what we meant, stating that the uncomplicated cases they have seen have all been very tractable. Our colleagues concur in this opinion.

From a study of histories of long-standing ulcer cases, one must come to the inevitable conclusion that each attack of ulcer symptoms is self-limiting, and not very differently influenced by vastly different modes of treatment or in fact an entire lack of treatment. Cole has demonstrated conclusively that each attack represents the development and complete healing of a separate and distinct ulcer, with subsequent ulcers often occurring at considerable distances from the previous ones. We have been able to confirm his observations roentgenographically, and pathologists have discovered multiple ulcer scars in the stomach and duodenum of patients with histories of many attacks of ulcer symptoms. The only logical inference to be drawn from these facts is that a peptic ulcer is an acute lesion, healing spontaneously and completely in a comparatively short time, and persisting or becoming chronic only as a result of the development of complications. The three marked complications of acute perforation, hemorrhage and stenosis are comparatively easy to recognize and their treatment is becoming standardized. The less acute but severely disabling "slow" perforations or near-perforations or the more or less acute complications in contiguous organs like the gall bladder or pancreas, resulting in deforming adhesions, scars, indurations or even abscesses or cysts are not so generally recognized. These, together with reflex or retrostaltic symptoms resulting from diseases of more distant organs, or entirely distinct symptoms from allergic, endocrine or nervous causes, as well as the occasional cases of carcinomatous degeneration, constitute the principal reasons for "intractable" symptoms.

Is it not therefore unreasonable, when a patient has symptoms which fail to be relieved by the usual measures found to be successful in ulcer cases, simply to call them "intractable" and institute treatment, medical or surgical, without first exhausting every effort to find out the reason for this intractability? In our experience such an investigation will invariably disclose a definite cause for the persistence of symptoms and will result in an intelligent medical or surgical attack upon the underlying causes. It is safest and most scientific, in the long run, to adopt the slogan "An intractable ulcer is a complicated ulcer."

Albert F. R. Andresen, Brooklyn.

SECTION IX—*Book Reviews*

(This section is open to contributions from any medical reader, whether or not a member of the Editorial Council).

Exploration Radiologique des Colons et de l'Appendice, Au Moyen des Solutions Floculantes; Images de Muqueuses, by Drs. Gorges Maingot, (Electro-radiologist, Laennec Hospital), Raymond Sarasin (former assistant in the Geneva and the Zurich Hospitals) and Henri Duclos (Assistant in Radiology, Laennec Hospital), with a preface by Dr. Antoine Béclère, (Head of the Medical Section, Academy of Medicine, Paris); Published 1935, by Masson & Company, Paris, 230 large, Atlas-style pages; price 200 francs.

THIS is the seventh of the series of monumental, epoch-making volumes concerned with Roentgen studies of special sections of the body, which recently have made the medical profession of the world indebted to its French colleagues and, peculiarly, to those audacious, yet understanding, publishers, Masson and Company. We say "audacious" because, so far as we have observed, no concern other than Masson & Company, has had the vision and the courage to comprehend the real need for authoritative atlases covering methods and results of skilled Roentgenography of the major body-systems and then has exhibited the patience, technical facilities and the artistic appreciation, requisite for carrying through to unrivalled fulfillment so extensive a plan. For, assuredly, as one handles and familiarizes himself with the individual volumes of this superb series, he cannot help but feel that, at the prices at which the books are sold, Masson & Company disregarded the ideas of *money-profit when they conceived and executed their* task. Rather, the work must have been inspired by a keen sense of our profession's need. Whatever may be the publication costs, the actual carrying through of the enterprise has been truly a "labor of love."

When we reviewed the two volumes which dealt with Roentgen studies of the Oesophagus, Stomach and Duodenum (*American Journal of Digestive Diseases and Nutrition*, Vol. 2, No. 6, Aug., 1935, p. 382) we expressed our sincere admiration for this series of special monographs and declared that the Roentgenologists of the world could not consider their educations completed unless they had been fortunate and had visited the Roentgen laboratories of Paris, or if that were impossible, they now had on their library shelves, the atlases published by Masson & Company. Our opinion has been supported by those who, recently, have sojourned in France and by those American clinicians and radiologists who have secured the volumes which previously we reviewed. In a sad situation are those who have availed themselves of neither opportunity!

Inspection of this, the most recent atlas, demonstrates that Drs. Maingot, Sarasin and Duclos have maintained the high, general standard of endeavor established by the Authors of the monographs which earlier were issued. For, in the Roentgen study of the colon, the appendix neighborhood and the appendix itself, they have set a mark which rarely will be approached; surpassed, we believe, never. Above all, in their discussions, constantly is emphasized that *clinical* radiology, not *technical* radiology or picture-making alone, has guided their efforts. Professor Béclère's "Preface" well puts it: *"Ce livre est l'oeuvre de trois medicins, excellents radiologistes!"* Would that, universally, it were recognized (and practiced!) that radiologists first must be trained physicians; technicians and light-and-shade interpreters only incidentally! In pathology, it does not necessarily follow that he who brings to the microscope's stage the most beautiful slides, must be the ablest histopathologist. Unfortunately, Roentgenology often seems to follow the positive, but wholly inaccurate and limiting, approach, that the making of striking films constitutes the goal of the radiologist. If nothing more, these atlases sent forth by our French colleagues, illustrate the new agenda of Roentgenography, viz. the *purposeful* exposure of subjects; the individualization of radiologic effort in the attempt to elucidate problems which history and clinical and laboratory examinations have suggested. This is far different, indeed, from submitting every subject to a routine formula of examination—be it suited or unsuited—and then endeavoring to *specialize* the interpretation. Such is a fundamental advance in making radiology an important adjunct to the physician's diagnostic armamentorium.

This volume dealing with Roentgen examination and interpretation of colon and appendix lesions, emphasizes the data which may be secured by the "triple-film" method. Prof. Forssell, Stockholm, pioneered the mode of Roentgen study of viscera whereby information was not limited alone to observations concerning contour, motor activity, changes in position, etc., but where definite manoeuvers were instituted with the object of demonstrating, Roentgenologically, abnormalities in or arising from the mucosa. That Forssell contributed a distinct addition to radiologic diagnosis, amply has been proved by the numerous studies recorded with respect lesions of the oesophagus, stomach and duodenum. In these viscera, Roentgen examination cannot be considered complete unless Forssell's technique has been exhibited and its results have been appraised by one expert in interpretation. Indeed, Forssell has given to the radiologist a method of diagnosis which enables him with regards oesophagus and stomach in a vast number of instances, to anticipate the data supplied by the gastroscopist—and this at little expense or risk to the patient. Not that Forssell's method ever will wholly supplant gastroscopy, but, undoubtedly, in numerous instances, it will give information respecting the condition of the gastric mucosa which is quite as dependable, from the clinical aspect, as is that supplied by even experts in gastroscopy.

Drs. Maingot, Sarasin and Duclos detail simply and completely the "new" radiology in respect the colon. In a series of quite normal subjects they enable us to compare and contrast the Roentgenograms secured after (1)—opaque enemata of 400-500 c.c. of a 12% solution of thorium-oxide suspension; (2)—evacuation of the opaque medium, and (3)—mucosal patterns after insufflation of the opaque substance. They exhibit illustrations of the special contrivances which facilitate introduction of the opaque medium and which enables the operator to perform adequate insufflation of the distended colon following evacuation of the primary opaque enema. Formulae of opaque media are given and cautions in respect types of case not suited to the procedure are listed. By easy stages, but not in kindergarden lessons, the reader is led from consideration of Roentgenograms which are those of normal persons to such as may be secured from subjects affected with various pathologic lesions.

There is introduced a very thorough, and withal, unique chapter graphically portraying the physiologic activities peculiar to the musculature of the colon and the effects which normal and abnormal responses produce Roentgenographically. The various "patterns" which are derived, together with their interpretations chemically, do much to familiarize the observer with the changes in such patterns, Roentgenographically where disease is present. The text which accompanies

these basic demonstrations is clear, crisp and informative.

However, much as the Authors rely upon changes in contour, tone, position, retention or in rapidity of evacuation of the colon as a whole or of special parts as exhibited radiologically, the chief endeavour of the book is directed towards exhibition of mucosal appearance when an opaque medium is "sprayed" upon it after the enema has been evacuated. These "relief" Roentgenograms, in subjects without or with, organic disease permit the production of striking films. Such films are by no means simply unique or curious technical achivements: in many instances, they demonstrate mucosal lesions wholly impossible to suspect or to prove in patients harboring no gross or deforming disease. When contour or position of the colon is changed by demonstrable affections, in addition to aiding in the better proof and localization of such, these "relief" films, often quite astonishingly, permit exhibition of the vast degree of associated mucosal change. The films submitted to demonstrate the wide variety of mucosal abnormalities, technically, are superb. Most striking "reliefs" and alterations in muscular action are exhibited subsequent to gaseous distention of the gut and then insufflation of opaque media and colon collapse upon evacuation of enemata. Indeed, only by this "3-film" method of Roentgen study of the colon do the radiologist and the clinician obtain an adequate conception of bowel architecture and of associated mucosal abnormalities. Very often, in fact, the Roentgen study demonstrates that gross motor changes of the gut's wall are wholly due to alterations from the normal in the mucosa. A text is included which definitely and intelligently points the "accidental" or artefact type of film and emphasizes the need for cautious interpretation.

Part 3 of this treatise deals with true colon lesions as shown by the "3-film" method of study. An excellent text and illuminating films are presented detailing Roentgen observations in instances of "Colitis," non ulcerative and ulcerative, with and without mucosal deformity, "Sigmoiditis," (in syphilis, both the tubal fibrosis and the gummatous or tumor-types are considered); "Tumors," including polyposis,—malignant and benign—(very striking are the mucosal patterns accompanying multiple poylposis); "Diverticula," with and without associated inflammatory tissue response, (very remarkable films, revealing altogether unexpected defects in colon walls, especially when peridiverticulitis complicates the lesion); "Tumors Extrinsic to the Colon," but producing alterations in contour and function, and "Tuberculosis,"—in this lesion, it seems that the insufflation technique is of the very greatest significance in demonstrating mucosal involvement not in any way recognizable by the now ancient opaque enema method alone. Through this entire Section dealing with organic colon lesions, the discussions and manner of presentation of illustrative material in every way exemplifies that Drs. Maingot, Sarasin and Duclos are clinicians and not merely radiologic technicians. It has never before been this reviewer's privilege to observe so concise, yet so complete, clinical and Roentgenologic exhibition of data.

Section 4—concerns itself with the Appendix, as a radiologic problem. The Authors admit that, from 1909, when Béclère first demonstrated the appendix by the Roentgen method, despite the careful, conscientous work of numerous Continental and American investigators (the pioneer work of Case in the United States is credited), the true significance of its visualization by films, still remains unestablished. Certainly, it would seem, that in "Chronic Appendicitis" alone is there justification for attempting radiologic study of the affection—and such study, not alone to prove whether or no the appendix lumen is patent, but chiefly to demonstrate visceral position, size, its relation to other abdominal organs and its effects upon the function of the colon, stomach and duodenum. When sub-acute or acute appendix disease is suspected, the Roentgen method of examination is not justified because of attendant dangers from its exhibition. This admirable clinical position taken by the Authors wholly has been supported by radiologists in other important laboratories.

The Section considers demonstration of the appendix by the oral and the enema routes of introducing opaque substances into the hollow viscera. Each has its advantages with respect not only the showing of the appendix on the films but of giving opportunity for exhibiting Roentgenologic abnormalities in tissues which are neighbor to the appendix. Often, indeed, the alterations shown in peri- and para-appendicular structures are of significance far greater than is proof that the appendix can or cannot be visibilized or of its length, position, fixation, etc. In the average patient, greater information concerning the appendix itself will be secured from opaque enemata but more Roentgen data concerning neighboring structures will become evident by the oral administration of the opaque substance.

The Authors present numerous film-reproductions showing the various types of appendix, the ability of the "organ" completely or incompletely to fill and empty, appendicular peristalsis, local or general dilatations, unusual positions, kinks, twists and their effects, appendicular diverticula (not nearly so infrequent as has been considered), intralumen calculi, the effects of diseased or unusually placed appendix upon bowel peristalsis—irritation and atony. There is a rational, conservative discussion of the "appendix syndrome" and its meaning to the clinician.

Section 4 concludes by what the reviewer regards is a too brief consideration of pathologic lesions of the terminal ileum, in which lesions all too-frequently the appendix is diagnosed the offender and is removed only to be followed by a series of disturbances due to progressive pathology in the small gut. Although the Authors exhibit several films detailing terminal ileum lesions in association with appendix abnormalities, there is not the complete radiological or clinical consideration of "terminal," "regional" or "non-specific ulcerative ileitis" (Crohn's syndrome) now so urgently —at least, in the United States—demanding recognition, elucidation as to nature and, above all, adequate treatment. It may be that the Authors plan later to present a separate work in which the Roentgenologic method is applied to lesions of the small intestine and in such they will give an appropriate discussion of Crohn's and other extremely important infectious, ulcerative and non-ulcerative, ileal disease and its serious consequences. Be that as it may, inasmuch as the early clinical manifestations of Crohn's syndrome generally result in a wholly non-curative appendicectomy, an operation which not alone may prove futile

but which may be followed by disastrous consequences in some individuals, it appears to the reviewer that, in this discussion of the appendix, the Authors could have wisely introduced the abundant Roentgen evidence which for several years—certainly in the United States—has been available. The reviewer strongly feels that, particularly in young subjects, no closed opinion regarding subacute or acute appendicitis existing alone, is possible until the clinician has excluded from being present "non-specific" ulcerative ileitis and tuberculosis. And of the two last named, the problem of their differentiation, clinically and radiologically, is by no means simple. Certainly, Roentgenograms alone are inconclusive.

But the above criticism by no means detracts from the value of the atlas being reviewed, especially when one limits the review to the Roentgenologic value of the material discussed as covered by the book's title. The Authors have given us a remarkable radiologic presentation of a specified field of endeavor and have supplemented it with accurate and conservative clinical comment. Technically, they have exhibited, strikingly, the possibilities of the new "3-film" method of Roentgenographic examination. The reviewer never has met with so complete and so brilliant an *arbeit* in any language. The library of no radiologic laboratory, of no Roentgenologist, of no clinician—physician or surgeon—whose major labors are concerned with abdominal problems, can be considered adequate unless it includes this volume contributed by Drs. Maingot, Sarasin and Duclos.

Frank Smithies, M.D.

Medical Papers, dedicated to Henry Asbury Christian, Physician and Teacher, from his present and past associates and house officers at the Peter Bent Brigham Hospital, Boston, Massachusetts, in honor of his sixtieth birthday, February 17, 1936. Edited and copyrighted by Robert T. Monroe, and printed by the Waverly Press, Baltimore, Md.

EXACTLY 1000 pages of excellent, valuable, original contributions, not appearing elsewhere, have been here assembled as a birthday volume to honor Dr. Henry A. Christian, teacher at some time to each of the authors. The subject material is well diversified and touches the following fields: cardiovascular disease, renal medical disease, metabolism, pulmonary disease, blood disease, parasitology, syphilis, general therapy, dermatology, medical economics.

Perhaps the least in numbers are the contributions to gastro-enterology; those that appear are, however, excellent. Halbersleben emphasizes the importance of gray stools as a manifestation of congestive heart failure. Golden finds that some of the symptoms accompanying calcified mesenteric lymph nodes are due to mechanical irritation of the small bowel by the nodes producing spasms. Burnett offers very considerable food for prolonged thought in an article entitled "The Intestinal Rate, Normal Nutrition and Health. New Principles for the Maintenance, Restoration and Control of Health." The general idea underlying Dr. Burnett's thesis and practice is "anabolic nutrition," induced by proper ways of eating and living. One of the principal guides is an estimation of the intestinal rate or the time it takes a marked sample of food to appear and cease appearing at the anus. Success is judged critically by the consistency and configuration of the stools. Assimilation of food is the most neglected factor in nutrition. His approach to the subject appears to be rational, well considered and free from faddism. A careful reading of his paper to appreciate the results obtained by regimentation of the colon is strongly advised. W. T. Vaughan contributes an enlightening paper on the mechanism and significance of the allergic response, which stimulates new viewpoints on this vastly important subject.

The book is beautifully bound and arranged. If its publication serves to set an example in "birthday" volumes, this new phase of publication practice must be a welcome one to the medical profession.

Beaumont S. Cornell, M.D.

SECTION X—*After "Hours"*

Raoul Bensaude of Paris

By

MARTIN J. SYNNOTT
NEW YORK, NEW YORK

NO man now living has done more than Raoul Bensaude to promote the specialty of proctology and procto-enterology on the continent of Europe. For many years he has been at the head of one of the world's foremost institutions specializing in diseases of the rectum and anus. His standing in Paris as a physician and diagnostician is comparable with that held in London by J. P. Lockhart-Mummery as a surgeon. The publication of his *Treatise on Recto-Colic*

Submitted November 26, 1935.



RAOUL BENSAUDE

Endoscopy (1) was an epochal event in the history of endoscopy and digestive pathology and placed Bensaude in the front rank of contemporary procto-enterologists. This important and original work was first published in 1919 and since that time there have been several editions.

EARLY MEDICAL CAREER

Bensaude was born a citizen of Portugal at Ponta Delgada, Azores, January 27, 1866. He went to Paris in 1886, and shortly afterwards began his medical studies, receiving his Doctor's degree in 1897. During these years he was fortunate in being a pupil of such eminent teachers as Millard, Fournier, Josias, Debové Achard, Hayem, Soca, and Lion. He worked hard, was always at the head of his class, and his graduation thesis won for him the title of "Laureate" of the Faculty of the Academy of Medicine (2).

For several years before his graduation Bensaude, inspired by Achard and Debové, had made bacteriological research his major interest, and in 1898, one year after obtaining his Doctor's degree, he was head of laboratories at the Faculty of Medicine, and in 1902 head of the clinical laboratory in the department of his teacher, Hayem. The work which he did during this period and in the next seven years, alone or in collaboration with Hayem, is of the greatest importance. Three achievements are especially noteworthy: the *discovery of paratyphoid* infections (rediscovered four years later, under the same name, by a German, Schottmuller of Hamburg); his remarkable graduation thesis on *serodiagnosis by agglutination of microbes;* and the discovery of the *serodiagnosis of cholera* (1898).

Bensaude had also found time for hematological research and we owe to him the remarkable works on *hemorrhagic purpura* (1897), *its chronic forms* (1905); *the relation of purpura and tuberculosis* (1908).

With Launois, he described *symmetrical adenolipomatosis with cervical predominance* (1899); later, this was named "Launois-Bensaude's disease."

ENTRANCE INTO FIELD OF GASTRO-ENTEROLOGY

As a result of Bensaude's first work with Soca (1900), Hayem (1905), and Lion (1907) and the inspiration and encouragement received from these eminent teachers, his inclinations, however, turned gradually more and more towards diseases of the digestive tract. In 1909 he was nominated Physician of the Hospitals and ten years later he was installed as head of the department of diseases of the alimentary canal in the Hôpital Saint-Antoine, the institution of his choice and the hospital pre-eminently of specialists of the digestive tract Here he has elected to remain ever since.

From the beginning of his medical career Bensaude was especially interested in the improvement of diagnostic procedures, particularly instrumental exploration, direct or indirect. He was one of the first to employ electrically lighted endoscopes for gastric and rectal examinations and to perfect the technique of the application of such apparatus and among the first to use a jointed or adjustable esophagoscope, externally lighted. He devised numerous rectal instruments which are still in popular use. In the field of radiology we owe to him the *use of a protective screen for radiological examinations* and especially the *use of creamy barium sulfate* for roentgen examinations of the digestive tract (with Ronneaux and Terrey, 1911).

Always alert to the importance of methodical and efficient organization of his hospital service, with a view to scientific research and teaching, Bensaude surrounded himself with carefully selected assistants whom he encouraged to work along highly specialized lines for which, in his judgment, they showed special talent. Several of the best known radiologists, electrotherapeutists, internists, and surgeons in Paris owe their start to Bensaude's inspiration and advice Among these are Charrier, associate of Gosset at the Salpêtrière, to whom Bensaude refers his major surgery and whose abdomino-perineal excision for cancer of the rectum and sigmoid compares favorably with that of the world's best surgeons; Marchand the radiologist; A. Lambling the electro-therapeutist, and numerous others. These men visit his clinic frequently and are always at his command for consultation and assistance.

Bensaude is an ex-President of the Paris Gastro-Enterological Society (1930), an honorary member of the Royal Society of Medicine, London, and of the American Gastro-Enterological Association.

MEDICAL PUBLICATIONS

In addition to the works already mentioned, Bensaude has published many masterful articles These include: *multiple cancerous strictures of the gastro-intestinal canal,* which he identified with linitis (with Ockinczyc, 1906); *idiopathic dilatations of the eso-*

phagus (1908); *bilocular syphilitic stomach* (with Béclère, 1911); *radiodiagnosis of cancer of the large intestine* (with Guénaux, 1917); *radiologic study of constipation* (with Constantin, 1918); *study of severe forms of recto-colitis* (with Cain and Antoine, 1919), etc.

In the United States, Bensaude is best known for his *Treatise on Recto-Colic Endoscopy* which has already been mentioned. It is an excellent interpretation of Bensaude's numerous and patient rectoscopic investigations. Unfortunately it has never been translated into English, owing to the expense involved in the reproduction of the numerous colored endoscopic plates, but in the latest edition the sub-titles and explanations of the plates are in English. This book is an invaluable guide and atlas to all students and teachers of diseases of the lower bowel.

Bensaude's more recent publications include: *Hemorrhoids and their treatment* (with P. Oury, 1930) (3); the first three volumes of a work on *Diseases of the intestines* (4) (in collaboration with his pupils), the third volume of which is only recently off the press and the fourth of which is to appear in 1936; a report to the surgical congress of 1934 on *Strictures of the rectum* (with A. Lambling) (5); a report to the congress of Plombières on *Ulcerous recto-colitis* (with J. Rachet, 1935); a report to the International Congress of Radiologists, Zürich, 1934, on *Indications for Roentgen treatment in benign ano-rectal diseases* (with Solomon and Marchand) (6). His chief collaborators are almost all departmental heads in the hospitals of Paris.

THE HOPITAL SAINT-ANTOINE CLINIC

Through the generosity of an American friend, Mr. Lucius Littauer of Gloversville, Bensaude was able to found a consulting service of proctology at the Hôpital Saint-Antoine. The number of attendances at this clinic now exceeds 30,000 a year, the only foreign rectal clinic comparing with it in attendance being that of St. Mark's Hospital in London, where the total number is about 10,000 a year. The Hôpital Saint-Antoine clinic is cosmopolitan and, as at St. Mark's, visitors from the four corners of the globe may be met there almost daily. Bensaude has founded a real school of diagnostic and medical proctology with numerous pupils, both French and foreign.

The clinic is practical and efficient in arrangement and equipment, although quite primitive in appearance compared with the proctologic examination room at St. Mark's (14).

Bensaude's method of digital examination is slow and very thorough and while making it he dictates to the historian in considerable detail. A complete sigmoidoscopic examination is done on every new case, but the 6 inch proctoscope is used in ordinary daily work. Illumination is secured from a forehead lamp, or a large operating room reflector so placed as to direct the light over the examiner's left shoulder. Electrically lighted instruments are used only in sigmoidoscopy.

Two tables in separate screened cubicles are reserved for Bensaude's exclusive use, so that while a patient is being examined in one compartment, another is being draped and prepared in the next, thus avoiding loss of time. A third compartment is used by an assistant, and a fourth is reserved mainly for electro-therapy. The patients are examined in the knee elbow or genupectoral position (right cheek resting on table), arms around (grasping) table, and voluntary lumbar lordosis is encouraged. This position is changed to the dorsal decubitus if abdominal palpation is indicated. An individual sheet of unironed unbleached muslin is used for draping each patient. The examiners use large-fingered heavy gloves, also two-fingered ones and finger cots.

Crystallized potassium permanganate is employed to control hemorrhagic oozing after minor surgical procedures in the peri-anal region; the application of a few crystals stops the bleeding immediately. Anesthetic oils are used only for underlying painful fissures (7, 14, 8). Unhealed peri-anal wounds, post-operative chronic infections, indolent anal ulcers, or ulcerated fissures are treated with a wet dressing of acidophilus culture (Lactomose-Pansement).

Bensaude does not find pruritus ani so troublesome as it is often reported in this country. Nearly all of his cases respond to soothing lotions or powders, local hygiene, removal of pathological conditions in the anus (9, 16, 18), relief of constipation (17) and toxic colon (15, 19). A favorite lotion is "Eau d'Alibour" the formula of which is:

℞	Sulfate of copper.....	1 gram
	Sulfate of zinc.....	4 grams
	Tinct. of safron.....	1 c.c.
	Spirits of camphor.....	10 c.c.
	Aq. dist. q. s. per.....	1000 c.c.

This preparation may also be prescribed in ointment form. Peri-anal injections with anesthetic oils, alcohol, or other agents are never used, nor is it found necessary to advise radiation or undercutting procedures.

Bensaude does not associate rectal diseases with focal infection to the extent that many Americans do, because the attendance at his clinic is so large that it would not be possible to examine teeth, tonsils, sinuses, and gall tracts. He is, however, familiar with the work done by B. B. Vincent Lyon of Philadelphia and recognizes the importance of his successful treatment of many procto-enterologic conditions of toxic origin by non-surgical biliary drainage (10, 13).

When the Frei test is positive, as is often the case in rectal stricture, the patients are treated with iodine by mouth or intramuscularly, but iodine is never used locally in the rectum.

Ulcers in the rectum and ulcerative colitis are treated with Laristine (Roche) a preparation of histidine, administered intramuscularly and from the use of which Bensaude claims many spectacular results. The American preparation is known as Larostidin-Roche.

As in America, ichthyol is freely used in treating anal and rectal inflammation. Bensaude's favorite prescription is:

℞	Ichthyol	50%
	Petrolatum	25%
	Lanoline	25%

Constipation is treated with mineral oil: one-half ounce 10 minutes before breakfast and, if necessary, a similar dose before the evening meal. Should the condition persist, psyllium seed (one-half ounce softened in water) is prescribed in addition to the mineral oil, to be taken in the mid-forenoon and mid-afternoon. In very severe cases the patient is instructed

to take a warm olive oil enema (one-half pint) at bedtime.

Amebic dysentery is treated with stovarsol: one or two compressed tablets before breakfast, every other day during 15 days each month. On the intervening days the patient is instructed to take 2 or 3 teaspoonsful of the following paste:

℞ Pure bismuth subnitrate
Charcoal
Simple syrup
Glycerine ..... aa 50 grams
Ipecac powder ..... 2 grams

RADIATION THERAPY

Bensaude makes extensive and apparently successful use of radium and the Roentgen ray in his therapy of rectal diseases. In this he differs from most American proctologists, whose experience with both of these agents has been disappointing.

Cancer: Radium in massive doses is used in the treatment of cancer of the terminal colon. It is frankly admitted that the patients frequently suffer great discomfort after its application and require morphine to allay the suffering, but many cures are claimed. *The danger of post-radium bowel obstruction is overcome by performing a preliminary colostomy before application of the radium.*

Fistula-in-ano: Bensaude's outstanding achievement with the Roentgen ray is in the treatment of fistula and fissure. He claims that radiotherapy, as he applies it, has cured 50% of chronic, multiple, complicated, recurring, previously operated cases of fistula-in-ano and caused a marked improvement in 30%. It is equally valuable in the treatment of unhealed, painful, chronic fissures. The fact that his cases have uniformly been without unfortunate sequelae and have yielded such remarkable results, justifies a detailed account of his technique (6).

Careful preliminary study of the fistulous canal is made by the injection of a substance opaque to X-rays (Lipiodol, bismuth paste, etc.) and plates are taken. In cases of simple fistula with superficial canal surgical excision is advised, X-ray treatment being reserved for the complicated variety with tortuous canals, where surgery is difficult and often unsuccessful.

The patient is given a total maximum dose of 2000 r., and 200 r. each session; it is preferable to prolong the dosage and weekly sessions are now the rule. An extremely penetrating radiation is not necessary, but there should always be strong filtration (0.5 m Cu. and 2 mm Al) in order to protect the skin, because of the frequent repetition of the dose. Two or three series of treatments are given, with an interval of two months between the first and second series, and four or five months between the second and third series. Following the immediate clinical improvement that almost invariably occurs, the lesion itself usually remains unchanged until the end of the first series of treatments. However, in some cases, it was noted that the suppuration decreased and even disappeared during the first course of treatment. Most frequently the discharge ceases a few weeks after the last irradiation. If suppuration persists after two months have passed, a second course of irradiations is instituted; if necessary, a third series four months after the second. The majority of cures are obtained after one to two series of irradiations.

The technique just described has no after-effects for men; it is different with mature women, since after treatment a temporary cessation of menstruation must be expected. In these cases a tangential irradiation of the perineal region must be employed and the dosage which might injure the ovaries must be reduced to the smallest quantity.

Anal Fissures: A number of cases with anal fissures and suppuration at the posterior pole of the anus were treated with X-rays. All were old recurrent fissures in which the usual methods (electro-coagulation, diathermy, anesthetic oils, sclerosing solutions) had failed. The great advantage was the almost immediate abatement of pain, sometimes from the first session. A small dose (225 r) was used weekly and the patients were examined every week in order to determine the necessity for further treatment. The irradiation is effected through an area including the anus, coccyx and sacrum. The use of a wide field seems justified by the neuralgic symptoms which almost always accompany anal fissures, causing Bensaude to regard this lesion as a trophic disturbance. The upper hemorrhoidal plexus sympathicus, the median plexus, and the roots of the sacral plexus are thus exposed to the action of the Roentgen-rays at the same time as the fissure.

As in the treatment of fistula, there was immediate improvement after the first treatment, which is explained by Bensaude as due to the action of the X-rays on the existent infectious element.

Pruritus Ani: Bensaude's attempts to alleviate pruritus ani by means of X-ray radiation have been no more successful than those made in the United States; only temporary relief has been secured. He irradiates the region around the anus, or the anus and vulva, and the coccygeal and sacral regions, with doses of 225 r once or twice a week, up to a total dosage of 1400 r. In cases with relapse, irradiation may be repeated two to three months after the first series, but after that X-ray treatment is abandoned for fear of skin troubles. For mature women, tangential irradiation only should be used.

Hemorrhoidal Thromboses: Acute hemorrhoidal prolapse, also called hemorrhoidal strangulation, is actually a phlebitis with thrombosis of the hemorrhoidal veins. For this reason, Bensaude claims that it is specially suited for X-ray treatment and that the earlier treatment is started the quicker will be the result. The most interesting point in this treatment is that it limits the duration of inflammation to a few days, while medical treatment often calls for weeks of absolute rest. Most competent surgeons condemn operative measures in the presence of strangulation, pari-anal edema, ulceration or sloughing for fear of grave complications, or even septicemia, and death.

Bensaude irradiates through a field covering the lesion, using as a first dose 150-225 r; after this first session the patient occasionally feels a return of pain and the anus seems to be the site of an intense inflammation, but usually there is no immediate reaction. The patient is re-examined four days after the first session and, if the results seem unsatisfactory, a second treatment is given. In a number of cases a cure was obtained only after six treatments at weekly intervals. Out of 17 irradiated cases, 14 cures are re-

ported, and in three cases considerable improvement occurred.

Anal Condylomata: Bensaude believes X-ray treatment is clearly indicated in anal condylomata and claims that it is specific.

Other Conditions: Although there are frequent relapses, Bensaude considers that Roentgen therapy is beneficial in purulent rectal inflammation.

In a case of diffuse recto-perianal angioma; X-ray treatment resulted in a marked retrogression of the angiomatous tissue. Local irradiation or irradiation of the spleen in hemorrhagic rectal inflammations produced only temporary results.

Contraindications: In two cases of *inflammatory stricture of the rectum,* a purulent breaking down of the lymphatic tissue of the fossa ischio-rectalis was observed following irradiation, necessitating an extensive opening of the whole region. Subsequently there were extensive purulent lesions with deeply penetrating channels and obstinate suppuration. In *rectal polyposis* the results of X-ray treatment are often merely temporary; surgical removal is preferable because of the frequent development of carcinoma.

ELECTRO-SURGERY

Diathermy, electro-coagulation, and electro-surgery are extensively used in Bensaude's clinic. In the French machines, the conducting cords or cables wind up inside the cabinet when not in use. Both the bipolar and monopolar currents are used, together with many unique types of active electrodes. Heavy lead negative electrodes are preferred to the flexible foil commonly employed in this country. The monopolar current is used for electro-coagulation of the mucosa in *rectal prolapse* or after unsuccessful Whitehead operations, and in the destruction of small *anal papillae.* In the treatment of *hemorrhoids* accompanied by bleeding, electrotherapy (diathermy) is used only in cases where there is pain; when the bleeding hemorrhoids are not painful, sclerosing solutions (urea and quinine 5%, two to three c.c. in each quadrant) are preferred. Operative procedures are reserved for the well-defined and extensive cases in which palliative treatment of any kind is manifestly unsuited; in such cases the electric snare and bipolar current are frequently employed (3).

BISMUTH SUBNITRATE THERAPY

Since Hayem's first work on the subject forty years ago, Bensaude and his other pupils have never ceased to call attention to the many remarkable properties of subnitrate of bismuth. They have made extensive research studies on its usage in gastro-intestinal pathology, showing the modification induced by bismuth in the gastric chemistry and other related subjects. They have reported its rational use in diarrhea and dysentery and gastritis; its successful employment in the treatment of organic diseases of the stomach and intestines; in spastic enteritis and colitis, in intestinal stasis, as a vermifuge, and in numerous other pathological conditions of the stomach and intestines (11).

Very large doses, up to 60 and even 70 grams daily, are frequently given, without symptoms of intoxication from the salt.

Bensaude strongly advocates subnitrate of bismuth in the treatment of constipation. He employs it in large doses only, as it is well known that small doses increase constipation.

Its use is not restricted to organic affections, as it seems to be equally beneficial in the neuro-vegetative diseases of digestive origin.

In the treatment of gastric ulcer the following method is used. In the morning, while fasting, the stomach is washed. A suspension of 20 grams of subnitrate of bismuth in 200 c.c. of lukewarm water is then introduced through the gastric tube, the tube being then rinsed with 50 c.c. of water in order to remove every trace of bismuth. The patient is put in such a position that the bismuth will be deposited precisely at the level of the ulcer. At the end of from ten to fifteen minutes the supernatant liquid is removed through the tube, the patient remaining in the same position for about half an hour. This treatment is given at first every day, then every other day, then every three days as long as the pains continue.

Many accidents—several of them fatal—were reported following the administration of creamy mixtures of bismuth subnitrate by mouth or rectum in the radiological study and exploration of the alimentary tract. In 1909 Bensaude and Agasse-Lafont studied the pathogenesis of these cases and reported that the danger of intoxication from the administration of large doses of the salt could be eliminated by observing certain rules: (1) It should not be administered to young children, on account of the intestinal flora facilitating the production of toxic nitric acid; (2) the *heavy* subnitrate of bismuth—a crystallized chemically pure salt—should be insisted upon, instead of the *light* variety, which is a mixture without a definite chemical composition, of different acidities, oxide of bismuth, etc.; (3) in order to insure purity, only the product of a well known chemical firm should be prescribed.

EPILOGUE

When Bensaude arrived in Paris, a youth of twenty years and a citizen of Portugal, he was a stranger in a strange land, and, like the Cuban, Albarran, before him, he had to struggle against all the obstacles encountered by foreigners in every country. His personality and charm of character were such that he easily overcame this handicap and his tact and unfailing good humor soon made friends of all his competitors (2). He has preserved the proverbial gayety and good nature of his Portuguese origin and no physician in Europe is more admired and respected by all who know him. He was loved first by his teachers, then by his confrères, then by his former assistants, and finally by his devoted pupils, who find in him a delightful and inspiring instructor, friend, and guide. His teaching attracts not only French students but many doctors from foreign countries, since his fame is world-wide. He brings to his work an ever fresh ardor, an ever lively curiosity as to work done in proctology in other lands, especially the United States. He is a linguist, reads and speaks English, German, Italian, and is familiar with the medical literature of all the ordinary languages. No distinction was ever more deserved than his post-war decoration with the Legion of Honor.

Although in his seventieth year, Bensaude's activity has in no way relaxed. A highly trained and experienced internist, he now devotes himself almost entirely to diseases of the rectum and the terminal portion of

the colon. His present rank at the Hôpital Saint-Antoine is Médecin Honoraire, but the men appointed to succeed him have voluntarily stepped aside and he is still in active charge of the clinic which he founded, where he may be found hard at work four mornings each week. Between clinic hours he is at his office at 139 Boulevard Haussmann, where his private consultations are held. Vacations do not appeal to him and he is seldom away from Paris except when he is called away for consultation or to address international medical congresses in other cities of Europe. More than anything else in life he enjoys work in his clinic where, surrounded by devoted assistants, consulted by his confrères, cheered by the frequent visits of former associates, and inspired by visiting physicians from foreign lands, he labors unceasingly for the good of his fellow men and the interests of science.

His private life has always been characterized by uprightness and kindness. Of him it may indeed be said, as was written years ago of a distinguished London surgeon, that he has been:

"Bold when sure,
Cautious in danger,
Kind to the sick,
Friendly with fellow workers,
Constant in duty,
Not greedy of gain." (12)

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SECTION XII—"*The Clinic*"

Amebiasis Associated with Carcinoma*

By

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A MARRIED woman, aged fifty-nine years, came to The Mayo Clinic on March 27, 1935. She had always been well until October, 1933, when a severe dysentery had developed three days after she had left Chicago, where she had spent several weeks at a downtown hotel. The dysentery had been associated with quantities of pus and blood, and she had passed dozens of stools every twenty-four hours. Endamoebae histolytica had been found in the stools on November 22, 1933. Fourteen grains (0.91 gm.) of emetine, which had been administered in the course of a month, had caused a cessation of the diarrhea. In January, 1934, there had been a recurrence of her trouble and at that time she had had acute protruding hemorrhoids, which had been removed. In July, 1934, Endamoebae histolytica again had been found in the stools, although they had been absent during the interim. She had had abdominal cramps. Some form of arsenic had been administered for two periods of ten days each. After this, the stools had been free of Endamoebae histolytica. She had been well until January, 1935, when loose stools again had recurred, but the outstanding symptom from then on had been severe abdominal cramps. These symptoms gradually had increased and lately they had been associated with some rumbling of gas in the abdomen.

Physical examination revealed a weak, somewhat debilitated woman, who weighed 119 pounds (54 kg.), and who was 64 inches (162 cm.) tall. There was general abdominal soreness and some tenderness. Two successive examinations of the stools in as many days revealed numerous Endamoebae histolytica. A proctoscopic examination revealed a reddened and congested mucous membrane. No discrete ulcers were apparent. Roentgenologic investigations revealed an annular defect in the middle of the transverse colon, which had all the features of carcinoma. Repeated urinalyses did not disclose any abnormality. Because of the findings of Endamoebae histolytica and because emetine had not been administered for more than a year, a total of 4 grains (0.24 gm.) of this drug was administered during each of two periods of three days. These periods were separated by an interval of one week. At the end of this time, another Roentgenologic examination of the colon did not show any change in the colonic deformity. Therefore, an obstructive resection of the transverse colon was performed on April 10, 1935. This disclosed an annular polypoid adenocarcinoma, grade 2, without involvement of the lymph nodes. Later, twelve tablets of treparsol were administered in each of two periods of four days. Recovery was uneventful and she was dismissed from the hospital on June 10, 1935.

She returned to this clinic September 9, 1935; at this time, she was feeling fine. She had regained her normal weight and did not have symptoms of intestinal dysfunction.

*Division of Medicine, The Mayo Clinic.
Submitted November 26, 1935.

Master Chart for Disease of the Biliary Tract*

By

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and
EILIF C. HANSSEN, M.D.
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IN our Out-patient Department Gall Bladder Clinic, we have found our Master Chart indispensable. A hospital rule makes it impossible to remove hospital charts from the Record Room except with special permission. Hence, the data concerning the patient's hospital stay are lost to the Out-patient Department records unless transcribed in some way. The Master Chart has solved this problem satisfactorily, for it provides a summary of the hospital chart for use when the patient returns to the Out-patient Department

*From Gall Bladder Clinic, Fourth Surgical Division, Bellevue Hospital.
Submitted March 16, 1936.

Gall Bladder Clinic for postoperative observation and biliary drainage follow-up.

The Master Chart for disease of the biliary tract is an especially arranged filing card for use in cases of disease of the gall bladder, bile ducts and liver. The card has been in use for the past ten years on the Fourth Surgical Division of Bellevue Hospital with great success. After being filled in, the Master Charts are filed and provide an immediately available detailed summary of each case. The original Master Chart, arranged in 1926, was made more complete about three years ago. This revised card (Plates 1 and 2) has met with the requirements of our Gall Bladder Clinic to date.

DESCRIPTION OF MASTER CHART

The Master Chart is 5x8" in size, made of filing card stock and printed on both sides. Space is provided for the recording of all data routinely of interest in the work-up of cases of biliary tract disease. The card is so arranged that whenever possible unnecessary handwriting is avoided by using a checking system in the interest of time saving and legibility. More than 75 observations can be recorded on the card.

On the face of the Master Chart, space is provided for name, address, age, nationality, sex, martial state, pregnancies, date of admission and discharge. The chief complaint with duration is stated briefly and described in detail later. Information regarding past illness (especially typhoid fever) and operations is then recorded. Under Present Illness, the predominating symptom, if pain, is described as regards location (right upper quadrant, epigastrium), character (dull, aching, colic), onset (gradual or sudden), radiation (to back or shoulder), aggravation, alleviation (hypo required). Associated symptoms are then noted, namely, nausea, vomiting, belching, distension, jaundice (persistent or transient), clay colored stools, fever, chills, soreness in upper right quadrant, loss of weight.

The findings on physical examination are included as follows: admission temperature, pulse, respiration, state of nutrition, presence or absence of jaundice, abnormal findings exclusive of upper right quadrant, upper right quadrant tenderness, rigidity or mass. Operative risk is also mentioned.

On the reverse side of the Master Chart are recorded laboratory data, operative notes, post-operative course, final diagnosis and condition on discharge.

The laboratory data include the cholecystogram report, describing whether or not the gall bladder was visualized, whether the gall bladder emptied normally, whether positive or negative shadows of stones were seen. The presence or absence of bile in the urine or feces is also noted, as well as the blood count. The preoperative biliary drainage findings appear as follows: amount of concentrated bile obtained, presence of cholesterol crystals or calcium bilirubinate pigment, or bile-stained pus cells, presence of free hydrochloric acid. The blood chemistry headings are the following: blood cholesterol, icteric index, direct or indirect van den Bergh tests, blood sugar, and non-protein nitrogen determination. Space is also provided for bleeding and coagulation time and blood Wassermann.

Details pertaining to operation include the following: pre-operative diagnosis, date of operation, name of operating surgeon, name of operation, operative findings (gall bladder normal, inflamed, dilated, or contracted, calculi in gall bladder, cystic duct, common duct, hepatic duct).

The card provides further space for post-operative complications, pathological reports, reports of culture of gall bladder bile, wall, cystic duct lymph node, final diagnosis, and condition on discharge.

HOW CARD IS USED

It is our custom to fill in the front of the card (history and physical findings) at the patient's bedside, preferably, prior to operation. The back of the card (work-up data, operative findings, pathological and bacteriological reports, post-operative course, final diagnosis) is completed soon after the patient's chart reaches the Record Room. The Master Chart is then filled by number after the name of the patient has been entered in a cross index alphabetical file.

ADVANTAGES OF THE MASTER CHART

1. It provides a detailed summary of a case of biliary tract disease.

2. This record is compact, easily filed, and readily available.

3. Such a chart, if properly used, guarantees a complete record of each case. A routine history may fail to elicit answers to certain questions of special interest to those interested in biliary tract disease. The Master Chart serves as an excellent check on the completeness with which a case is worked up. At a glance, it is easily noticed that a patient failed to have a cholecystogram, biliary drainage, blood chemistry, or bile culture.

4. In hospitals not using the Unit Chart System, the Master Chart is ideal for use in the Out-patient Department in the follow-up treatment of patients operated on in the hospital.

5. The card is so arranged that a minimum of time is required to record a large amount of information.

SUMMARY

1. A summary card, called the Master Chart of biliary tract disease, is described.

2. It has been used in the Gall Bladder Clinic of the Fourth Surgical Division of Bellevue Hospital for the past 10 years with increasing usefulness.

3. The card includes information on more than 75 observations of special value to those interested in the study of the disease of biliary tract. This information is recorded by a checking system, whenever possible, in the interest of legibility and economy of time.

MASTER CHART OF BILIARY TRACT DISEASE

Fourth Surgical Division
Bellevue Hospital

No. .....
Positive—Check
Negative—Zero
Not Done—Dash

Name ..... Age ..... Nationality ..... Adm. ..... Disch. .....
Address ..... Married ..... Sex ..... Pregnancies .....
Chief Complaint: ..... Duration: .....
Past History: Illnesses: ..... Typhoid: .....
Operations: .....

Present Illness:

1. PAIN a. Location: R. U. Q. ....., Epigastrium .....,
b. Character: Colic ....., Dull aching .....,
c. Onset: Gradual ....., Sudden .....
d. Radiates to back: ....., Rt. *shoulder* .....
e. Aggravated by .....
f. Relieved by .....

2. Nausea .....
3. Vomiting .....
4. Belching .....
5. Distention .....
6. Jaundice .....
Persistent ....., Transient .....
7. Clay colored stools .....
8. Fever .....
9. Chills .....
10. Soreness .....
11. Loss wt. ..... lbs. in .....

PHYSICAL EXAMINATION ON ADMISSION: T....., P....., R.....

1. General: Obese ....., average ....., Emaciated ....., Prostrated (Colic) .....
Jaundice: Present ....., Absent .....
Abnormal findings (Head, Neck, Chest—Heart and Lungs, Extrem., K. J.)

.....
.....
11. Local: Rt. upper quadrant: Tenderness ....., Rigidity ....., Mass .....
.....

OPERATIVE RISK: Good. Fair. Poor.

PLATE 1

Cholecystogram:
Normal Visualization .....
Faint Visualization .....
No Visualization .....
Normal Emptying .....
Delayed Emptying .....
Calculi .....
Other X-rays: .....
Urine: Bile present ....., absent .....
Feces: Bile present ....., absent .....
WBC and Diff. .....
Biliary Drainage: Date .....
Gastric free HCL .....
Amount of "Concentrated Bile" .....
Cholesterol Crystals .....
Bilirubin Calcium Pig. .....
WBC — Bile Stained .....
Culture .....
BLOOD Cholesterol .....
Icterus Index .....
Van den Bergh .....
Direct .....
Indirect .....
Blood Sugar .....
Blood Urea .....
Bleeding Time: ..... Coag. Time: .....
Blood Wassermann .....

Pre-op. Diag. .....
.....
Date of Operation .....
Operator .....
Operation: .....
Cholecystectomy, Below upwards .....
Cholecystectomy, Above downwards .....
Cholecystectomy ..... Choledochostomy .....

FINDINGS:
Normal gall bladder .....
Inflamed .....; Dilated .....; Contracted .....
STONES present in
Gall bladder .....; Cystic duct .....
Common duct .....; Hepatic duct .....

Drainage used: .....

COMPLICATIONS .....

PATHOLOGICAL REPORT .....
.....
Gall bladder bile:
Micro.: Cholesterol crystals .....
Bilirubin calcium pig .....; WBC .....

Culture:
Gall bladder bile .....
Gall bladder wall .....
Gall stones .....

FINAL DIAG.: .....
.....
Discharged: Imp. ....., Unimp. ....., Dead.
Signature .....

PLATE 2

Moniliosis of the Respiratory and Digestive Tracts

By

OSCAR BERGHAUSEN, B.A., M.D.
CINCINNATI, OHIO

FUNGI form a large heterogenous group of plants, (all lacking in cholorophyll), which not infrequently cause saprophytic and pathogenic changes in man. Probably the term *monilia* should be restricted to that species of which *Monilia candida Bonorden* is considered the type. Much confusion has arisen by classifying many organisms in the group monilia. Under certain environmental conditions many representatives assume a yeast-like appearance, but under suitable conditions true ascospores are formed, placing them definitely in the *eremascaceae.*

In man these organisms occur in the digestive tract of normal individuals. The majority are saprophytes which have found a suitable substratum for growth and multiplication, and through the enzymes and toxins secreted, may interfere with the normal functions of the organs. They may cause mild to severe lesions. They gain entrance as a rule through the respiratory tract, alimentary tract, genitalia and the skin, and may involve any organ of the body.

Most physicians are familiar with "thrush," as it involves the tongue and pharynx of children or cachetic adults, causing creamy patches usually on the tongue. The organism is now called *monilia albicans*, reproducing by blastospores but also forming filaments of short irregular units which may give rise to large, oval cells appearing as short terminal chains called conidia by some, blastospores by others. It is probable that the disease is not always caused by the same organisms only some of which liquefy gelatin. The following is a typical instance of infection in an adult:

CASE REPORTS

Case 1. Mr. E. J., aged 74; no history of previous illness; was exposed to wet inclement weather for twelve hours. Following this he developed aching pains and a cough. When seen three weeks later he had a temperature of 103, pulse of 100 and a respiration of 38, with symptoms of bronchitis marked by scattered rales over the left base. The heart sounds were irregular with a distinct systolic murmur over the base.

The man was in a good state of nutrition for his age, weighing 160 lbs. Cataractous changes were present in both eyes; the nasal passages were clear; a few poor teeth remained and the soft palate, uvula and tonsillar area were covered by a greyish membrane which did not extend over the base of the tongue. A few submaxillary lymph nodes could be palpated bilaterally. The hearing was normal. The thyroid was not enlarged. The abdomen was not involved, there being no enlargement of the spleen, liver nor kidney. He had no pain and was rational.

Smears and cultures showed the presence of *oidium albicans, endomyces albicans*—a specias of monilia. The blood count showed marked anemia, leucocytosis with marked increase in the number of lymphocytes. The red cells totaled 2,500,000, the hemoglobin 52%, the white cells numbered 35,100. The differential count showed the presence of 10% polynuclear cells, 66% lymphocytes, 3% transitionals, 1% large mononuclears, 3% myelocytes, 12% lymphoblasts, and 5% immature lymphocytes. The urine was cloudy, amber in color, specific gravity 1.024, a trace of albumin, no casts, no sugar.

The temperature continued to fluctuate between 99 and 103. There was distinct improvement locally through the use of 1% gentian violet and weak permanganate solution. However the general condition became worse, the patient dying, eleven days after admission to the hospital, from the effects of pulmonary complications following his attack of influenza, chronic myocarditis, chronic interstitial nephritis and generalized arterio-sclerosis.

The organism isolated by Alfred O'Neil showed pearly white colonies on solid media; developed acid but no gas with dextrose agar; produced neither acid nor gas in mannite, saccharose and lactose agar; did not liquefy gelatin; produced no lead sulfide in liquid media containing lead acetate and formed hyphae in broth containing carrot thus differentiating it from ordinary yeast cells or saccharomyces.

An instance of mycotic infection occurring late in the course of an attack of influenza pneumonia followed by empyema is seen in the following clinical history. Undoubtedly the organism was originally a harmless invader, but later found the proper soil and environment for rapid growth. The lung tissue subsequently obtained at autopsy was examined microscopically and was found to resemble a typical tuberculous lesion; subsequent animal inoculation was negative for tuberculous infection however.

Case 2. Dentist, aged 37, admitted to hospital on November 14, 1933, with diagnosis of acute influenzal bronchitis, involving the left upper and right lower lungs chiefly. The temperature varied between 100 and 102.6, pulse 124. The urine showed one plus albumin, no casts; the blood count was 3,860,000 red blood cells, the leucocytes numbered 11,100 of which 86% were polynuclears. On November 23, 1933, the leucocytes numbered 37,650 of which 89% were polynuclears. Pneumococcus, type IV, was isolated from the sputum. The first X-ray examination of the chest made on November 22, 1933, showed the entire right side to be markedly dense especially marked in the lower two-thirds. The heart was displaced to the left. On the left side was peribronchial thickening, otherwise the left side was negative. An exudate probably purulent in nature was suggested on the right side. A preliminary drainage tube was inserted and on December 31, 1933, rib resection for right sided empyema was performed. The patient improved and from January 17th to 23rd the temperature was within normal limits. On January 25th the condition again became worse and the patient died on February 10, 1934.

The post mortem examination revealed:

1. Lobar pneumonia in the stage of gray hepatization involving the right upper and middle lobes with early abscess formation in the former.

2. *Localized necrosis of a segment of the ileum one and one-half feet above the ileocecal valve with associated*

Submitted February 13, 1936.

fibrino-purulent peritonitis producing low grade intestinal obstruction.

3. *Acute diverticulitis of Meckel's diverticulum.*
4. Right fibrino-purulent uretero-pyelitis (right), less marked on the left.
5. Thrombo-phlebitis of right innominate vein.
6. Toxic changes in viscera.
7. Pulmonary congestion and edema with possible hypostatic infiltrate in the right lower lobe.
8. Cardiac dilatation.
9. Right chronic obliterative pleuritis (incomplete).
10. Thoracotomy wound.
11. Edema of skin and soft tissues, elbows and ankles.

The microscopic examination of the lung tissue showed alveolar exudation with typical tubercle formation and areas of necrosis with giant cell formation.

The pneumococcus type IV was isolated by Alfred O'Neil from the sputum during November, 1933. In February, 1934, repeated daily examinations of the sputum failed to reveal the presence of tubercle bacilli, but did repeatedly reveal the presence of yeast-like organisms. Possible extraneous sources of this organism were carefully ruled out; cultures were made on Sabourand's and ordinary media. Pure cultures developed acid but no gas in dextrose and saccharose agar. Hyphae developed in simple broth and broth containing carrot. Inoculations into the nasal mucous membranes of a guinea pig and subcutaneous inoculations of a guinea pig gave negative results. The organism was classified as monilia albicans and was isolated from the sputum, the lung at autopsy and the pus obtained from the ureter at autopsy. Lung tissue containing hyphae obtained at autopsy and treated with 3% sulphuric acid, was inoculated into two guinea pigs. After five months one animal died but showed no evidence of tuberculosis or other bacterial infection; the other animal remained perfectly normal.

Torula is a name incorrectly used as a synonym for moniliae. Dodge (1) classifies torula as belonging to the *cryptococcus*. He mentions two groups, the one isolated from tumors and at one time considered a cause of cancer; the other group includes species such as *cryptococcus histolyticus*, which may infect the respiratory tract of man and lead to chronic meningitis and eventual death. In the differential diagnosis of atypical epidemic encephalitis, cerebral neoplasm or tuberculous meningitis, the examination of the spinal fluid for torula organisms should be borne in mind. Clinical characteristics are gradual onset with headache and stiffness of the neck, disturbances in sleep, amblyopia and diplopia developing later, associated with symptoms on the part of the respiratory tract and enlargement of the lymph glands. Sawers and Thompson (2) describe such a case of chronic meningitis due to torula as having followed the development of a granuloma that developed from a razor cut. These authors also mention a case of typical chronic meningitis as reported by Johns and Attaway, in which trauma over the scapula was followed by a deep mycotic infection which had healed many months before the onset of meningitis.

In the following abstract of a clinical history published elsewhere (3) the writer mentions a torula infection arising in the tongue, eventually leading to death by inanition after a course of eleven months.

Case 3. Man, aged 28, a laborer in a steel plant, suffered an injury to the anterior part of the tongue June 20, 1926, when a piece of hot steel flew into his mouth. When I first saw him on January 11, 1927, he had become emaciated, complained of weakness and pain on eating from the infection of the tongue. His temperature was 100 and the pulse rapid. Stereoscopic X-ray pictures of the chest showed bilateral infiltration not typical of tuberculosis. Cultures from the tongue showed the presence of torula histolytica. The blood count showed 4,900,000 red cells, 80% hemoglobin, 3,850 white cells including 54.5 per cent polynuclears, 30.5 per cent small and 5 per cent large lymphocytes, 1 per cent mast cells, 3.5 per cent eosinophiles and 5.5 per cent transitionals.

The patient improved somewhat after the injection of two doses of 0.6 gm. Neo-salvarsan and 2 grain doses of quinine sulfate given three times daily. A third intravenous injection of 0.3 gm. Neo-salvarsan made him worse and he subsequently died of inanition on May 17, 1927. Quinine sulfate and sodium iodine given internally over a prolonged period seemed to be of no benefit. An autopsy was not permitted.

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ABSTRACTS

CLINICAL MEDICINE

REID, MONT R., M.D., POER, D. HENRY, M.D., AND MERRELL, PAUL, M.D.

A Statistical Study of 2,921 Cases of Appendicitis. J. A. M. A., Vol. 106, pp. 665-6 69, Feb. 29, 1936.

From a series of 2,921 cases admitted to Cincinnati General Hospital from January 1, 1915, to January 1, 1934, the following has been determined:

Appendicitis is a disease of adolescent and young adult life, and is more common in the male than in the female. The time elapsing between the onset of the symptoms and the admission to the hospital averaged 3.8 days and was found to be too long for proper surgical treatment. The symptomatology in these cases is as follows:

1. Abdominal pain located in the epigastrium or around the umbilicus.
2. Localization of the pain over McBurney's point.
3. Tenderness on palpation in the right lower quadrant.
4. Nausea and vomiting.
5. Muscle spasm and rigidity usually, but not always present.

The temperature in simple acute cases was rarely over 100 degrees F., but in cases of gangrenous appendicitis and peritonitis it averaged between 102 degrees and 104 degrees F. The temperature in children with simple acute cases sometimes went as high as 103 degrees Fahrenheit. The leucocyte count varied with the severity of the infection and the presence or absence of complications.

Approximately 60 per cent of the acute cases were admitted during the first attack, and approximately 40 per cent of all cases were admitted after rupture of the appendix. The use of purgatives was found to increase the incidence of perforation and to lessen the patient's chances for recovery. Over 98 per cent of the deaths from appendi-

citis were due to the complications accompanying perforation.

The mortality rate in acute unruptured appendicitis was 0.86 per cent; with abscess formation, 11.4 per cent; with peritonitis, 33.9 per cent.

The conclusion was reached that the time elapsing between the onset and the treatment was too long; that the death rate for complicated cases when treated by immediate surgery, is too high. It is therefore believed that the Ochsner treatment in complicated cases is superior.

Francis D. Murphy, Milwaukee.

POTTER, M. G., M.D.

Observation of the Gall Bladder and Bile During Pregnancy at Term. J. A. M. A., Vol. 106, pp. 1070, March 28, 1936.

The fact that many pregnant women complain of abdominal distress and pain in the right upper quadrant prompted this investigation. In 390 cesarean sections the gall bladder was inspected, palpated and aspirated. Upon some of the cases a bacteriologic and chemical analysis of the bile was made.

The following results were obtained:

1. 60 per cent of cases had cholesterol concentrations between 100 and 400 mg. per one hundred c.c.

2. 60 per cent had bile salt concentrations between 300 and 400 mg. per one hundred c.c.

3. 62 per cent had a bile salt: cholesterol ration between 1:1 and 3:1. In 7 per cent the ration was reversed (1:2, 1:3).

4. The greater the concentration of cholesterol, the greater the number and more constant was the presence of calcium, bilirubin and cholesterol crystals.

5. There was no relationship between the bile salt: cholesterol ratio and the constancy of the crystals found.

6. Only 26 per cent showed no evidence of cholesterol or calcium bilirubin crystals.

7. The five cases in which positive cultures were obtained showed a concentration under 300 mg. per cent. Of these cases four showed cholesterol or calcium bilirubin crystals.

8. In 20 cases the blood-bile cholesterol ratio was 1:1 in 8 cases; 1:2 in 8 cases; 1:3 in 1 case; 1:4 in 2 cases; 1:5 in 1 case.

The conclusions were reached that 75 per cent of normal gall bladders are distended at term. An adequate fat intake would be advisable to prevent gall bladder distress. Bile stasis in the gall bladders of pregnant women is common. Bacterial invasion is rare. Metabolic dysfunction associated with functional motor disturbance and stasis rather than infection or mechanical pressure seems to be the forerunner of biliary disease in women. Hypercholesterolemia exists at term. Postoperative nausea and vomiting appeared to be reduced by release of pressure within the gall bladder. There was no definite ratio between the blood-bile cholesterol concentrations demonstrated.

Francis D. Murphy, Milwaukee.

KRAEMER, MANFRIED, M.D., AND ASHER, MAURICE, M.D.

The Association of Erythremia and Duodenal Ulcer. Am. Jour. Med. Sci., p. 234, Feb., 1936.

The theory of Morris, Schiff and Foulger that erythremia was caused either by excessive secretion of a blood forming hormone by the stomach which they named "Addisin" or by susceptibility of the bone marrow to stimulation by addisin. It is noted that a year later they concluded this hemopoietic factor secreted in the normal stomach was identical with the "intrinsic factor" of Castle.

Morris et al treated a case of erythremia associated with a duodenal ulcer by lavage of the stomach 3 to 4 times weekly. On this treatment the patient's blood count fell from 10 to 5.3 millions —a few months later, without lavage, it rose again to 10.2 millions. Boyd concluded that polycythemia bore a causal relationship to duodenal ulcer and Wilbur and Ochsner studied the cases of erythremia at the Mayo Clinic and found 8% in 143 case records compared with 2% in 200 control cases of hypertension.

The writers report two cases illustrating the association of polycythemia with duodenal ulcer, one of which quickly passed from observation while the other patient co-operated and was given bi-weekly gastric lavage for three months. He was given a bland diet and alkalies. He was relieved of his ulcer symptoms but not of his polycythemia.

The Authors write that it is possible they did not perform gastric lavage frequently enough as Oerting and Briggs lavaged their patients four to six times daily and thus produced a reduction in red blood cells. The Authors make a rather startling and radical suggestion that "should a patient with erythremia and duodenal ulcer associated show a marked reduction in erythrocyte count after gastric lavage, gastrectomy might afford permanent cure of both afflictions."

Allen Jones, Buffalo, N. Y.

REICHLE, HERBERT S.

Primary Tuberculous Infection of the Intestine. Arch. of Pathol., Vol. 21:1, Jan., 1936.

A report of an undoubted case of primary tuberculous infection of the intestine of probable bovine type of origin is given, together with a brief review of the controversy started by von Behring in 1903 when he stated that a large percentage of all cases of tuberculosis originated in childhood by infection through the intestinal tract. Although now generally agreed that the bovine tubercle bacillus is virulent for man and that an ingestion form of primary tuberculous infection exists, still its exact percentage of occurrence is a matter of dispute.

The Author concludes from a study of the literature that infection with the bovine variety of the tubercle bacillus is unusual outside of England, Scotland and Wales, except when the infected person has used an infected dairy product. Infections of this sort in the United States and Canada are rare because of the general use of Pasteurized or boiled milk, and when found are usually traced to cows infected with tuberculosis. He quotes Wilson as stating in 1932 that 5.2 per cent of all deaths caused by tuberculosis in England and Wales were due to the bovine organism. This is because raw milk is generally used in the British Isles and a study by the Scotch Board of Health, for instance, demonstrated the presence of tubercle bacilli in 20 per cent of the milk tests.

N. W. Jones, Portland, Ore.

BUTT, HUGH R.

Myasthenia Gravis: A Study of Postmortem Observations, Including the Demonstration of Gram-Positive Bacteria (Streptococci) in and Between the Muscle Fibers. Arch. of Pathol., 21:1, Jan., 1936.

The Author reports the study of seven cases of myasthenia gravis in which muscle tissue taken immediately after death from many locations in the body showed many gram-positive diplococci, which were taken to be streptococci, within and between the muscle fibers in sections stained for microorganisms. An equal number of control cases showed no microorganisms in the muscle fibers when studied in a similar manner.

The apparent association of preceding acute infections with the onset of myasthenia gravis is commented upon, and the suggestion is made that the underlying cause of the disease may be a type of infection which becomes localized in the muscles and that these bacteria may be the origin of the toxin which produces its characteristic fatigability.

N. W. Jones, Portland, Ore.

CAPRIO, FRANK S.

An Outbreak of Botulism in New Jersey. J. A. M. A., Vol. 106, pp. 687-689, Feb. 29, 1936.

Botulism is a comparatively rare disease, especially on the Atlantic coast, but it is rarely possible that some cases have been confused with encephalitis, acute poliomyelitis, toxic ophthalmoplegia and various types of food poisoning.

The outbreak described here occurred in March, 1935. A family of five be-

came ill suddenly, after eating a jar of home preserved peppers. The diagnosis was made early because of the typical symptomatology and history. Two members died before the botulism antitoxin was available and the other death occurred after the administration of the antitoxin.

The incubation period in these cases varied from two to sixty-nine hours after the ingestion of the toxin. The symptoms were blurred vision, diplopia, blepharoptosis, photophobia, lassitude, weakness, obstinate constipation, offensive breath, disphagia, inability to articulate, drowsiness, normal or subnormal temperature, vomiting with eructation of gas, and mental awareness.

The laboratory was unable to culture the bacillus botulinus in any of the cases.

Death in all three cases was due to respiratory failure.

Necropsy of the three cases revealed: 1. Acute toxic poisoning; 2. chronic passive congestion of all organs; 3. hemorrhage into the stomach.

The impression of the pathologist was atoxic neuronophagia. The poison seemed to come from the toxin of the bacillus of botulism.

Treatment was both specific, consisting of the administration of botulinus antitoxin A and B, and symptomatic.

Francis D. Murphy, Milwaukee.

EXPERIMENTAL PHYSIOLOGY

EKLAND, CARL M., AND REIMANN, HOBART A.

The Etiology of Amyloid Disease, with a Note on Experimental Renal Amyloidosis. Arch. of Pathol., 21:1, Jan., 1936.

The Authors discuss briefly the various theories of causation of amyloidosis of the secondary type; the type characterized by large deposits of typical amyloid substance in the liver, spleen and kidney which follows in the course of chronic diseases.

Experimentally in five rabbits they produced extensive amyloidosis of the kidneys by the intramuscular injection of 5 c.c. of a 10 per cent solution of sodium caseinate three times a week until shortly before death. Two animals died in eight months, one in eleven months, one in thirteen months, and the fifth in seventeen months after the first injection. Evidence of illness was usually noted two or three months before death. The latter occurred with the signs and symptoms of nephrosis or nephritis and uremia. Four had minimal changes in the liver and spleen while the fifth, which lived the longest, had extensive amyloid changes in these organs as well as in the kidney.

Hyperglobinemia developed in each rabbit soon after the beginning of the experiment and continued until death. Total protein content of the blood was increased early but sank below normal levels after renal damage and uremia appeared. The experiments support the view that chronic hyperglobinemia is an important factor in the etiology of amyloidosis of the secondary type.

N. W. Jones, Portland, Ore.

KELLER, ALLEN D., AND D'AMOUR, MARIE C.

1. *Ulceration in the Digestive Tract of the Dog Following Intracranial Procedures; Preliminary Study.*
2. *Protection by Peripheral Nerve Section of the Gastrointestinal Tract from Ulceration Following Hypothalmic Lesions, with Preliminary Observations on Ulceration in the Gastrointestinal Tract of the Dog Following Vagotomy.*
3. *Ulceration in the Digestive Tract of the Dog Following Hypophysectomy. Arch. of Pathol., 21:2, pp. 129, 165, 186, Feb., 1936.*

In a series of studies on ulceration of the digestive tract in dogs, following experimental lesions of the brain stem, Keller and Keller and D'Amour found hemorrhagic states in the mucosa of the stomach in a high percentage in one series and characteristic crater formation in the mucosa of the body of the stomach in another series. In no instance were gross or histologic evidences of the latter lesions associated with the former. The hemorrhagic states occurred spontaneously after complete destruction of the anterior portion of the hypothalamus. Craters were never found unless part of the anterior portion of the hypothalamus was intact. This suggested, in the author's opinion, that the hemorrhagic states were precipitated by the activation of the sympathetic outflow (posterior portion of the hypothalamus) and the craters by activation of the parasympathetic outflow (anterior portion of the hypothalamus).

Acute and chronic ulceration in the stomach followed vagotomy alone only when the dogs were subjected to yard conditions during the winter months and were not found in dogs protected by cage regimen. In a series of dogs in which bilatetal vagotomy was performed before a chiasmal lesion was produced, hemorrhagic states were found but no ulcers occurred. In another series the abdominal portions of the sympathetic chains were removed prior to the placing of a chiasmal lesion and in this group typical gastric and duodenal ulcers were formed whereas no hemorrhagic states were to be found.

Hemorrhagic states and gastric and duodenal ulcers were found in a percentage of cases after hypophysectomy, and were identical with those which occurred after chiasmal lesions. The authors present evidence which indicates that the ulceration was precipitated not because of the lack of hypophyseal secretions but because of a neighboring neural derangement, possibly intraventricular stimulation, as a result of opening the third ventricle during the operation. The studies are detailed: many protocols of experiments with photographs and microphotographs of the anatomical material are given.

N. W. Jones, Portland, Ore.

ROENTGENOLOGY

SCOTT, WENDELL G., M.D., AND MOORE, SHERWOOD, M.D.

A Method of Roentgen Diagnosis of Non-Opaque Foreign Bodies in the Esophagus. J. A. M. A., Vol. 106, pp. 906-908, March 14, 1936.

The most frequent non-opaque or radiolucent object to become lodged in the esophagus is a piece of unossified bone from a fowl or fish. The next most frequent object is a button or a bolus of food. These objects usually may be found lodged at the level of the suprasternal notch, but also at the introitus, at the level of the left bronchus, and at the diaphragm.

The initial symptom is usually a gagging or choking, followed by a feeling of apprehension, dysphagia, adynophagia, exaggeration of the movements of swallowing, and drooling.

The roentgenographic procedure is to take anteroposterior and lateral views first. If this does not visualize anything, the patient is placed in front of the fluoroscope and given a thick suspension of barium sulfate in water, and carefully observed to determine whether there is a deviation or division of the stream or a filling defect. After this, it is noted whether any of the barium is clinging to the foreign body.

Next, a film of the entire esophagus is made. This is done by having the patient drink a very thin, watery solution of barium through a glass tube in short, quick swallows. Exposures are made in both the anteroposterior and the right anterior oblique positions. The barium coats the esophageal walls and produces a constant filling defect. It also coats the foreign body, revealing it as a collection of opaque material.

Francis D. Murphy, Milwaukee.

ABDOMINAL SURGERY

LEWISOHN, RICHARD, M.D.

Recent Advances in the Surgical Treatment of Chronic Duodenal Ulcers. J. A. M. A., Vol. 106, No. 9, pp. 684-687, Feb. 29, 1936.

The surgical treatment of gastro-duodenal ulcers is at present the subject of much controversy. In the past fifty years many procedures have been ad-

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A miniature working model of an Irradiated Pet Milk plant was displayed at the annual meeting of the American Medical Association in Kansas City.

Several thousand physicians saw there, with much interest, the actual operation by which Pet Milk is produced. The concentration to double richness, the irradiation, homogenization and sterilization were all definitely demonstrated.

These processes produce in Pet Milk the following qualities of definite interest to the gastro-enterologist.

1 Uniform double richness, which facilitates the inclusion of more milk in the diet.

2 Freedom from all bacterial life — a safeguard against infection or intestinal irritation from this source.

3 A more ready digestibility because of the formation of small, soft, non-irritating curds.

4 Hypo-allergic effect on the patient sensitive to milk.

5 Richness in vitamin D created by irradiation with ultra-violet rays.

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vocated from gastro-enterostomy, local resection, sleeve resection, to partial or subtotal gastrectomy.

The Author believes that partial or subtotal gastrectomy is preferable to gastro-enterostomy. He believes that the occurrence of gastrojejunal or jejunal ulceration and the persistence of symptoms is too high in gastro-enterostomy. The patient frequently is not improved, the hyperacidity persists, and the pylorospasm frequently remains after the operation. He believes the percentage of occurrence of gastrojejunal ulcers following gastro-enterostomy is between 34 and 50 per cent. The mortality rate for re-operation in cases of gastrojejunal ulcer is about 20 per cent, while the mortality for subtotal gastric resection varies from 1.5 to 3.1 per cent in the hands of well trained surgeons. This surgical procedure shows the frequence of gastrojejunal ulcer to be about 7 per cent.

The Author says that in his follow-up clinic complete restoration to health is the rule, and complaints of gastric distress the exception.

Francis D. Murphy, Milwaukee.

CULLEN, THOMAS S., M.D.

Intestinal Obstruction Due to a Hole in the Mesentery of the Ascending Colon. J. A. M. A., Vol. 106, No. 11, pp. 895-898, March 14, 1936.

Intestinal obstruction due to abnormal openings in the mesentery is probably the rarest of all etiological factors. Cases of this malady have been reported by Edwards, Brown, Cutler, Elston, McWhorter, Juad and Hamaker.

According to Edwards, there were only two cases of obstruction of the large bowel ever reported. This present case is one in which there was an opening in the mesentery of the ascending colon.

The history of this case in brief is as follows:

A doctor's son, 11 years of age, who had always been in excellent health except for attacks of abdominal pain of short duration and relieved by vomiting, for the past two or three years. He had also complained of pain in the side of the abdomen after running, and of pains in the legs after any strenuous exercise. Three months previously, he complained of severe abdominal pain, lasting for five minutes and occurring after playing football.

In the past three months he had appeared more tired than usual, turned pale on several occasions and almost fainted.

The day before this attack he had felt the same as usual. That night it was noticed that he was snoring in an unusual manner. He awoke at 2:30 the next morning with slight abdominal pain, which gradually became worse, until at 6:30 A. M., when his father saw him, the pains were acute paroxysmal and generalized. Examination revealed no localized tenderness and no muscular rigidity. Some nausea was present, but attempts to vomit were unsuccessful. Operation was decided upon immediately.

A grid-iron incision was first made, and bluish-black bowel was seen. A *mid-line incision was made immediately* and a hole about two centimeters in diameter was found in the mesentery of the ascending colon. Through this a loop of large bowel had passed and become gangrenous and distended.

Corrective surgical measures were instituted and recovery was uneventful except for severe abdominal distention and a pharyngitis and bronchitis of moderate severity.

Francis D. Murphy, Milwaukee.



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The Specially Prepared
Colloidal Cream of Aluminum Hydroxide
. . . . for the ACID FACTOR in Peptic Ulcer

Granting other primary factors, it is now acknowledged that the most important factor and immediate cause of Peptic Ulcer is the acid digestion of the affected tissue. Desirable ant-acid therapy is, therefore, indicated.

Creamalin presents a most desirable ant-acid therapy. It possesses a much higher combining power than the soluble alkalies, (one volume combining with fourteen volumes of one-tenth normal hydrochloric acid in one hour by physical fixation) without the attendant dangers of alkalosis

Creamalin provides prompt relief of pain, nausea, and pylorospasm. (Usually within twenty-four hours). Creamalin therefore should be employed in all cases of Peptic Ulcer, especially those that have been refractory to previous therapies.

Write for reprints reporting on its use by the continuous drip method. Material for clinical evaluation available on request.

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Mead's Oleum Percomorphum

During the hot weather, when fat tolerance is lowest, many physicians have found it a successful practice to transfer cod liver oil patients to Mead's Oleum Percomorphum.

Due to its negligible oil content and its small dosage, this product does not upset the digestion, so that even the most squeamish patient can "stomach" it without protest.

There are at least two facts that strongly indicate the reasonableness of the above suggestion: (1) In prematures, to whom cod liver oil cannot be given in sufficient dosage without serious digestive upset, Mead's Oleum Percomorphum is the anti-ricketic agent of choice. (2) In Florida, Arizona and New Mexico, where an unusually high percentage of sunshine prevails at all seasons, Mead's Oleum Percomorphum continues increasingly in demand, as physicians realize that sunshine alone does not always prevent or cure rickets.

Mead Johnson & Company, Evansville, Indiana, invite you to send for samples of Mead's Oleum Percomorphum for clinical use during the summer months to replace cod liver oil. Adv.

Have you thought of doing without barbiturates in your practice?

Many physicians have found that Sedormid completely and safely replaces the barbiturates. Sedormid is not a barbiturate, and yet it is a dependable, gently-acting sedative and hypnotic. It doesn't have the sledge-hammer, sleep-enforcing effect of the barbiturates. Instead, it allows sleep to come in a more natural way, by merely overcoming tension and apprehensiveness,—in a word, by promptly removing the barriers to sleep.

*SEDORMID 'Roche'

As a day-time sedative 1 to 2 grains three times a day. Internists find it incomparable for quieting the super-charged nervous system in cases of hyperthyroidism. Neuropsychiatrists prefer it for systematic sedation in anxiety states and other neurotic manifestations. The thin undernourished patient with "nervous" indigestion or with gastro-intestinal hypermotility, the woman in menopause with vasomotor instability, the menstruating woman with nervous irritability—all these, and others that fall in the same category, receive gratifying benefit from small day-time doses of Sedormid. Bromides, in ordinary doses, are too weak; barbiturates are too strong; Sedormid, neither a bromide nor a barbiturate, meets the indication precisely.

As a hypnotic 4 or 5 grains about 20 minutes before sleep is desired. Indicated in all cases of insomnia, regardless of the cause.

Packages. *Tablets, 4 grains each, in boxes of 10 and bottles of 100.*

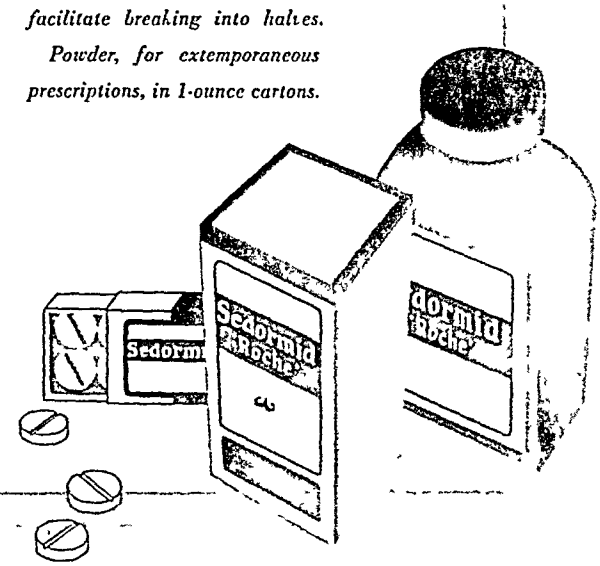
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New report shows

BRAN HELPS MAINTAIN IRON SUPPLY

of the human body

THE November, 1935, issue of the *Journal of the American Dietetic Association* reports a comparative study of bran and egg-yolk, a known rich source of iron.

The subjects were healthy young women. The conclusions developed by the experiment were *"that the iron of egg-yolk and of bran can be used with equal efficiency for the maintenance of iron equilibrium in the human adult."*

This study continues a series of researches, conducted over a period of five years, in which new contributions to our information on bran have been made. Some of these tests have confirmed the value of bran as a safe laxative food for normal people. Others have demonstrated that it does not lose its effectiveness with continued use.

Further independent tests on men have indicated that the "bulk" in bran is often more effective than that found in fruits and vegetables.

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ALL-BRAN may be served as a cereal, with milk or cream, or cooked into muffins, breads, etc. Sold by all grocers. Made by Kellogg in Battle Creek.

The natural food

THAT CORRECTS CONSTIPATION

due to insufficient "bulk"



BLAHD, M. E.

"Surgical Indications for Peptic Ulcer and Its Surgical Management." S. G. O., 62:203-212, Feb., 1936.

To the usual positive indications for surgical treatment of peptic ulcers (perforation, pyloric obstruction, and, occasionally, severe and uncontrollable hemorrhage) the author adds the deep penetrating type of ulcer. This latter type, he believes, is impossible to cure medically and when recognized by X-ray examination (which is usually not difficult) should be subjected to operation. The type of operation preferred is subtotal gastrectomy and a rather convincing proof of its superiority is offered. Analysis of statistics is presented showing a larger percentage of immediate cures, there is practically no secondary mortality, the difference in primary mortality is more than compensated by mortality of secondary operations, jejunal ulcer is practically never encountered, and the patient is immeasurably more comfortable in all ways including the liberality of his diet.

A detailed illustrated description of the operation is included in the article.

J. Duffy Hancock, Louisville.

BARTLETT, WILLARD, JR., M.D., AND BARTLETT, ROBERT W., M.D.

Perforation of the Gall Bladder with Massive Intraperitoneal Hemorrhage. J. A. M. A., Vol. 106, pp. 615, 616, Feb. 22, 1936.

Perforation of the gall bladder is in itself a comparatively rare lesion, but when accompanied by massive hemorrhage it is an event of extreme rarity. Only two cases have been reported in the literature since 1900.

This is the report of a case of a 65 year old woman who entered the hospital with the complaints of abdominal pain, distention of the abdomen and constipation.

In the past year the patient has had two acute attacks of epigastric pain radiating to the interscapular area and relieved by vomiting. Two days before admission, the patient had a similar attack not relieved by vomiting and followed by progressive distention, not relieved by enemata. The patient had seven attacks of vomiting in the three days, and one bowel movement shortly after the onset of the attack; there was no passage of the stool or flatus after that.

Physical examination of the patient upon entering the hospital revealed an obese, dehydrated woman with severe abdominal distress. The abdomen was distended and presented generalized tenderness, no rigidity, but dullness in the flanks. Pelvic and rectal examinations were negative. Temperature—104.4; pulse—102; respiration—40; B. P.—165/20; hemoglobin—62 per cent; R. B. C.—3,396,000; W. B. C.—20,000.

CONTROL



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Petrolagar is a palatable emulsion of pure liquid petrolatum, (65% by volume) and number One Silver White Kobe Agar-agar, accepted by the Council on Pharmacy and Chemistry of The American Medical Association for the treatment of constipation

Petrolagar Laboratories, Inc., 8134 McCormick Blvd., Chicago, Ill.

The Schilling count showed segmented forms 78 per cent, stabs 10 per cent, lymphocytes, 11 per cent, and monocytes, 1 per cent.

X-ray of the abdomen revealed distention of the large intestine and cecum.

Operation revealed a tear on the under surface of the gall bladder from which venous blood was welling. The peritoneal cavity was filled with about two liters of fluid blood.

The patient progressed for a short time, but then took a turn for the worse, and rapidly succumbed to a broncho pneumonia.

Autopsy revealed a rupture of a gall bladder, the seat of a chronic cholesystitis with cholelithiasis.

Francis D. Murphy, Milwaukee.

HUEPER, W. C.

Spontaneous Arteriosclerosis in Rats. Arch. of Path., 20:5, 708, Nov., 1935.

In general it is agreed that experimental arteriosclerosis has been produced only in rabbits and to a less extent in guinea pigs, that such lesions have not been produced in other laboratory animals. Spontaneous arteriosclerosis in rats is supposed to be of infrequent occurrence. Hueper reports the finding of arteriosclerotic lesions in the branches of the pulmonary artery in 12 rats out of a series of 75. In the arteries of no other organs were such changes observed. These rats were adult and their death had been produced experimentally in a manner which could not have caused degenerative arterial changes. The lesions were found mostly in the large and médium sized branches near the points of bifurcation. Multiple plaques were usually present. The majority of lesions consisted of cone shaped calcified foci, covered by endothelium, projecting into the lumen. They were located in the subendothelial tissues and frequently extended into the media which showed local hyaline degeneration. There were at times indistinctly outlined streak like formations which involved only the media, and, again, small hyalinized areas containing calcifications were observed involving only the media. The intima covering the foci was usually thickened and the seat of cellular infiltration. There existed more or less hypertrophy of the media in many of the smaller arterial branches. Complete obliteration of the lumen was observed once. The deposition of lipoids in the walls of these vessels was not studied.

N. W. Jones, Portland, Oregon.

HUET, P.

Prolapse of the Lowered Colon in a Case of Resected Rectum. Operative Cure by Hystero-Hyero-Pexie (Utero-Sacral Fixation). (Prolapsus du côlon abaissé chez une amputée du rectum. Cure opératoire par hystéro-hyéro-pexie. Fixation utéro-sacrée). J. de Chir., Tome 46, No. 6, p. 363-366, 1 Fig., Sept., 1935.

Having a case of his own to deal with, the author describes a technique capable of yielding good results where prolapse of the lowered loop of colon occurs following amputation of the rectum for cancer. Several fruitless operations having been tried previously and the classic method of the obliteration of the pouch of Douglas has been judged impracticable. The author conceived the idea, for this case, of utilizing the uterus and broad ligaments for filling in the pelvic excavation. For this purpose he fixes the fundus of the uterus to the promontory after transverse incision of the peritoneum, in front of the bony prominence after separation of the fatty pelvic tissue and denudation of the fibro-periosteal layer which cover the anterior surface of the sacrum. The posterior surface of the fundus is fixed to the fibrous presacral tissue by three bridges of linen thread. The pouch of Douglas is obliterated by the fixation of the round ligaments to the superior inlet. On the right, the whip stitch is continued and closes the breech completely. On the left the whip stitch is stopped at the point where it encounters the pelvic colon, thus aiding the latter in its easy descent into the pelvis. Four or five separated sutures drawn together fix the pelvic colon to the broad ligament, closing all communications between the large cavity and the pouch of Douglas, henceforth excluded. The superior lip of the incision of the presacral peritoneum is sutured to the anterior surface of the fundus uteri thus peritonealizing the suture of the utero-sacral fixation.

Cure has been maintained since two and one-half years.

The test of time attributes to this operation a curative value. It is applicable to the non-hysterectomized woman when all possibility of pregnancy has disappeared; it may not be practiced until after the menopause; if the uterus conserves dimensions allowing it to be brought without rough tearing in contact with the sacrum. It is an exceptional procedure, but on occasion, a definite cure.

Pierre Smith and Thomas Farmer, Montreal, Canada.

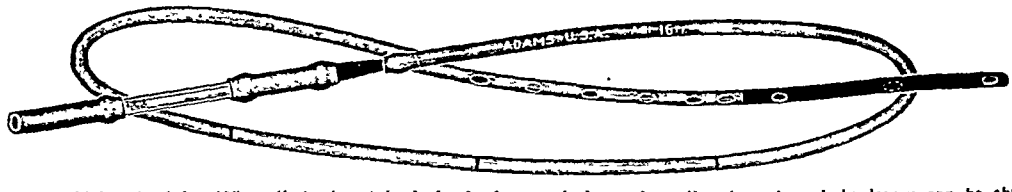
HUNT, V. C., AND BUDD, J. W.

Transduodenal Resection of the Ampula of Vater for Carcinoma of the Distal End of the Common Duct. S. G. O., Vol. 61, No. 5, pp. 651-661, Nov., 1935.

The incidence of malignant disease of the periampullary region can not be stated with very great accuracy since such conditions in that situation have received but little attention until recently. Certainly the number of cases attached surgically is a very low estimate of their incidence. One-third of all new growths of the bile ducts originate in the lower end of the common duct and practically always they are carcinomas.

The age incidence of malignancy of the periampullary region corresponds with the age incidence of malignancy elsewhere. The clinical manifestations of such conditions are usually those of common bile duct obstruction and of duodenal ulceration with bleeding and

X-RAY TIP WEIGHTED DUODENAL TUBE



Note the nine eyes, which extend for 10" so that when tube is in duodenum, drainage from the stomach and duodenum can be obtained at the same time; also that the end for 3½" is processed to appear opaque in X-ray or fluoroscopic examinations, and that the tip is weighted; thus the tube is easily carried into the duodenum. French Scale sizes 14 and 16 only. Each in box.

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OVALTINE used as a liquid diet owes much of its reputation as an invalid food to the fact that it will frequently nourish where ordinary foods are badly borne.

Because of its high nutritive value, its ready digestibility, its palatability, Ovaltine now occupies a prominent place in the dietetic treatment of disease.

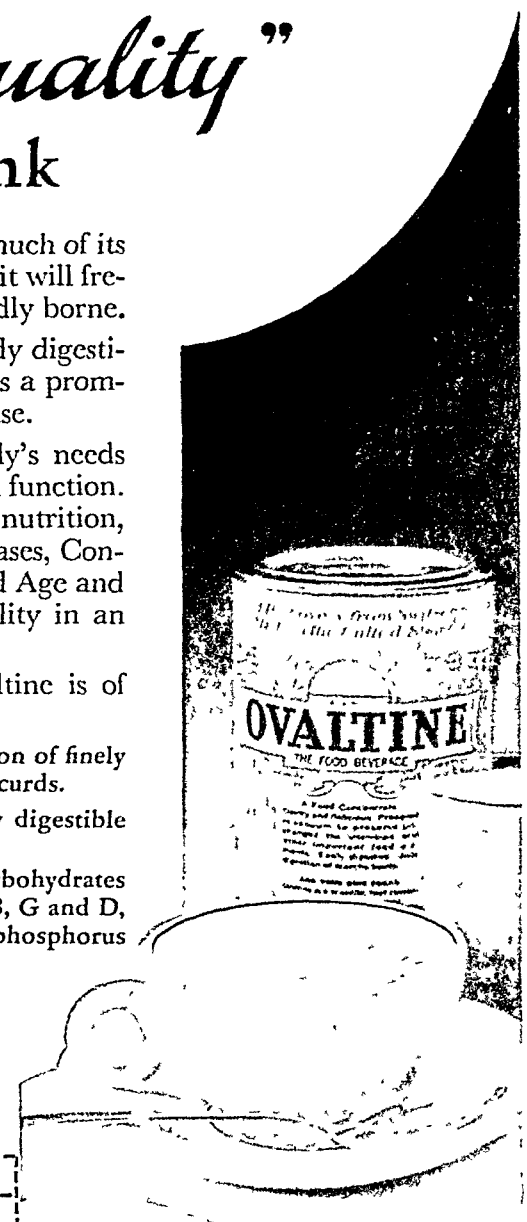
Ovaltine provides nutriment for the body's needs for energy, and material for its structure and function. It is useful in such conditions as Child Malnutrition, Fevers and Infectious Diseases, Wasting Diseases, Convalescence, Before and After Operations, Old Age and wherever it is desirable to supply food quality in an easily digested form.

There are three main reasons why Ovaltine is of value in such cases.

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secondary anemia. Diarrhea has been a frequent symptom.

Most carcinomas of the periampullary have been found at autopsy to be removable surgically. Death usually occurs before metastases appear. The mortality following radical extirpation of carcinoma of the periampullary region ranges between 30 and 70 per cent.

The modern one-stage operation of excision of the growth and reimplantation of the ducts carries the lowest mortality. Palliative operations whereby biliary obstruction is relieved by some anastomatic procedure between the gall bladder and upper gastro-intestinal tract, even though executed with considerable risk are often productive of much palliation.

The author reports one case of successful transduodenal resection of the ampulla of Vater for carcinoma of the distal end of the common duct and abstracts of seventeen additional cases. Seven figures, two tables and a bibliography accompany the article.

Nelson M. Percy, Chicago.

GLENN, F.

Colostomy of the Transverse Colon. S. G. O., Vol. 61, No. 5, pp. 629-634, Nov., 1935.

The author points out that transverse colostomy as an emergency operation, or as a preliminary measure in the treatment of lesions of the lower sigmoid and rectum possesses certain advantages over lumbar or inguinal colostomy. First, the bowel is always freely mobile and may be delivered into a right rectus incision with a minimum of trauma; the bowel content at that point is non-irritating to the skin. Second, a transverse colostomy is far removed from the operative field and does not endanger the asepsis of any procedure on the bowel distal to it. Peritonitis is a frequent and serious complication of procedures on the lower sigmoid and rectum.

Transverse colostomy is not a major procedure. Through a muscle splitting high right rectus incision a loop of transverse colon is elevated and held in place by means of a glass rod passed through a rent in the transverse mesocolon. The closure of the wound is designed (1) to anchor the intestine, (2) to prevent the peritoneum from tearing, (3) to isolate the rectus muscle, and (4) to avoid herniation of the bowel. The posterior leaf of the sheath of the rectus is closed and sutured to the bowel wall with medium silk sutures. The anterior leaf of the sheath of the rectus is now sutured to the peritoneum, and in the case of obese patients, the skin is drawn down to the fascia. Vaseline gauze is placed about the bowel and covered with the same type of dressing; after 36 to 48 hours the bowel is opened. If it is deemed necessary to decompress the bowel at the time of operation that may be done by introducing a needle into it after a purse string suture has been put in place. A catheter or glass tube may be inserted in the same manner. A large sized glass rod is inserted through a short incision in a tenia opposite the mesenteric attachment of the bowel, if immediate decompression is not deemed necessary. After six or seven days that tube is removed. The glass rod is usually removed before the drainage tube is withdrawn, but it may be left in place several days longer if the loop tends to retract or if it is desired to prevent any of the fecal stream from passing into the distal segment of bowel. The patient soon learns that a degree of constipation enables him to reduce the number of evacuations of his bowels to one or two a day. A dressing of absorbent material guards against soiling.

When it is desired to close the colostomy that may be accomplished by incising the skin about the colostomy, then carefully dissecting away the subcutaneous tissues and fascia until the peritoneum is seen, after which the excess tissue is cut away and the opening in the bowel closed transversely. If there has been a herniation of omentum or bowel about the colostomy, it may be necessary to deliver that part of the transverse colon outside the abdomen. Such a closure must be considered as contamination of the peritoneal cavity but peritonitis or abscess formation rarely occurs. A subcutaneous drain is recommended. After closure of the colostomy the patient is given nothing by mouth for 24 hours, then only clear fluids for 48 hours after which full diet with mineral oil may be given.

Nelson M. Percy, Chicago.

MOOREHEAD, M. T., AND MCLESTER, JAMES S.

Abdominal Apoplexy. J. A. M. A., Vol. 106, pp. 373-374, Feb. 1, 1936.

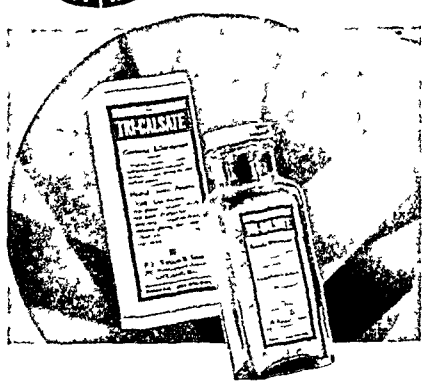
Fatal nontraumatic hemorrhage into the peritoneal cavity of a male, without malignancy, is a rare vascular accident. Several cases of massive intraperitoneal hemorrhage have been reported, but most of these have resulted from trauma, cancer or disease of the female generative organs. Three nonfatal surgical cases have also been reported.

Two unusual cases of hemorrhage into the peritoneal cavity are reported here. The one case was being treated for vascular hypertension, Bright's disease, and syphilis. The patient died suddenly after twenty-seven days' hospitalization with symptoms of internal abdominal hemorrhage. Autopsy of



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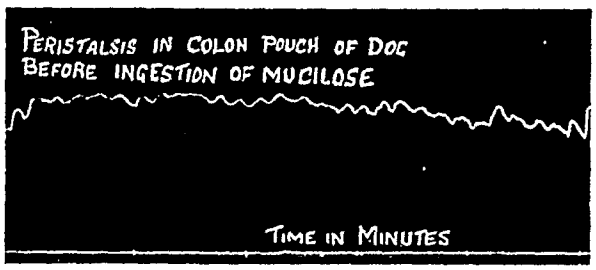
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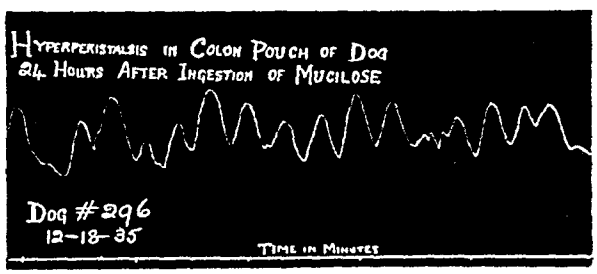
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this case revealed atherosclerosis of the gastric artery with rupture at the junction of the left and right branches. The other case was one admitted for the treatment of pulmonary emphysema and myocarditis with the complaint of dyspnoea and precardial pain of several years duration. The patient died on the forty-sixth day after admission, also with symptoms of internal abdominal hemorrhage. Autopsy revealed a ruptured, dissecting aneurism of the superior mesenteric artery.

Francis D. Murphy, Milwaukee.

STUDLEY, HIRAM O.

Percentage of Weight Loss. J. A. M. A., Vol. 106, pp. 458-461, Feb. 8, 1936.

The surgical treatment of peptic ulcer has greatly reduced the mortality rate, especially of those cases which ruptured into the peritoneal cavity. The mortality rate has, however, not been reduced below 10 per cent in uncomplicated cases of peptic ulcer. The purpose of this article was to show the relationship between weight loss and recovery from surgically treated ulcer cases not complicated by rupture.

The weight loss was determined by subtracting the pre-operative weight from the weight before the onset of the peptic ulcer. Of fifty patients studied, the weight loss was determinable in forty-six of them. It was found that in the group whose weight loss was approximately 20 per cent, the mortality rate was 33 and one-third per cent, while in those who lost less, the rate was 3.5 per cent.

Because of the aforementioned observations, it seems that another major complication has been added to those of peptic ulcer: namely, loss of weight, and should therefore receive the indicated pre-operative preparation.

Francis D. Murphy, Milwaukee.

LAPLACE, R., AND BROCARD, H.

Ulcérations gastriques consécutives à l'injection perisplanchnique de substances toxiques. C. rend. Soc. Biol., Paris, 119:112-113, 1935.

The authors injected alcohol, lead acetate and nickel sulphate around the left splanchnic nerve in guinea-pigs. Post-mortem examinations showed haemorrhagic or ulcerative gastric lesions. Similar lesions were produced by either ligation or electrical stimulation of the nerve.

M. H. F. Friedman, Montreal.

SURGERY OF THE LOWER COLON AND RECTUM

HOWET, FR. (Brussels).

Pathogenesis and Surgical Treatment of Prolapse of the Rectum. (Pathogénie et traitement chirurgical du prolapsus du rectum). J. de Chir., Tome 45, No. 6, pp. 877-908, June, 1935.

Following a study of five cases of complete prolapse of the rectum observed in the service of Lenormant, the author reviews briefly the progress made during the past 30 years in the understanding of the pathogenesis and in the treatment of this condition. According to Cruveilhier-Ludloff there are four anatomical varieties:

1. Invagination of the mucosa *(prolapsus ani)*
2. Invagination of the inferior portion of the rectum through the anus *(prolapsus ani et recti)*
3. Invagination of the superior part of the rectum into the inferior portion *(prolapsus recti)*
4. Precipitation through the anus of an invagination of the colon *(prolapsus coli invaginati)*.

Etiological data. As for hernia the etiology of prolapse of the rectum is governed by effort either single and strong (delivery), or repeated and weak (constipation), diarrhea, alternating constipation and diarrhea, irri-

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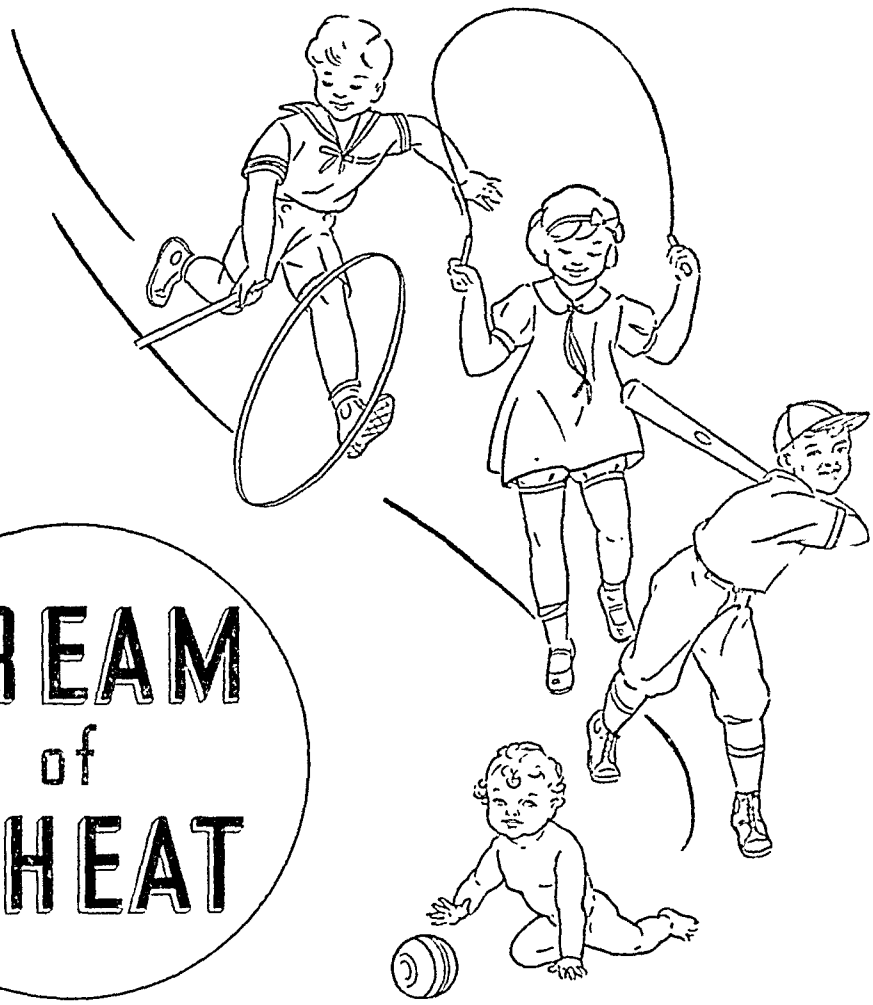
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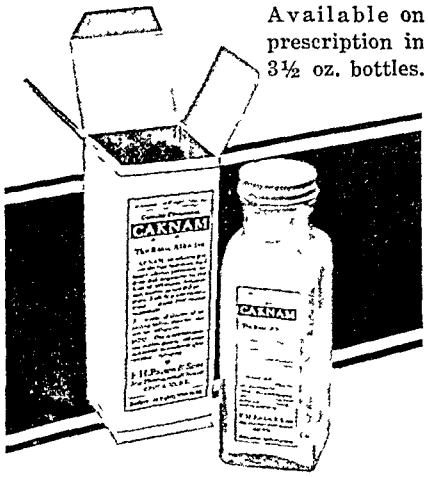
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tated rectum, tenesmus, hemorrhoids, intestinal worms, efforts of micturition, urethral stricture, hypertrophy of the prostate, stones in the urinary bladder, chronic cough.

Morbid anatomy of rectal prolapse. Not well understood. If the lesions of the rectum have been established with accuracy due to examination of the resected portions, those of the neighboring parts have not, except incompletely, due to a lack of sufficient autopsy material. However, two factors stand out clearly by reason of their constancy: the abnormal mobility of the rectum and the excessive depth of the pouch of Douglas. These two anomalies are essential to and characteristic of a rectal prolapse.

Pathogenesis. The pathogenesis which should be looked at from the anatomical point of view is based on two orders of facts:

1. The normal mode of fixation of the rectum;

2. The exact anatomical lesions observed in those suffering from prolapse of the rectum and, in particular, the lesions affecting the normal means of fixation of the rectum (Lenormant).

The Author observes that these two points are not yet well established and he expounds the different theories relative to the pathogenesis of these lesions. He concludes thus: "From this, we believe that to close the pouch of Douglas and to prevent all possibility of invagination of the rectum should be the two essential steps of the operative cure of rectal prolapse."

Operative treatment of the rectal prolapse. Methods of cutting off the prolapsed portion. I. *Resection by scalpel.* The Author describes the procedure most commonly employed, that of Mikulicz. He explains the different modifications of this method and the results obtained by different surgeons. This procedure, however, maintains an appreciable mortality, frequent recurrences due to the persistance of the sac and frequent strictures due to suturing. These three arguments condemn the resection (Lenormant). The Author concludes that in view of the serious consequences which may ensue it is unwise to resect the prolapsed rectum, except: (1) When it is irreducible or (2) when there is danger of introducing in the pelvic cavity a septic focus *e. g.* where the rectum is gangrenous or very ulcerated or where there is a strangulated hydrocele.

II. *Method of keeping the reduced rectum in place.* The theories of pathogenesis have served as the basis of these methods.

1. Procedures to reconstruct the pelvic floor: (a) Shortening or contraction of the sphincter ring; (b) Substitution of the sphincter by the method of Thiersch; (c) Strengthening of the sphincter by strips of muscle; (d) Myorraphy of the *levatores ani;* (e) Muscular or aponeurotic strips strengthening the pelvic floor.

These different methods are reviewed and commented upon.

2. Procedures which have for their aim the suspension of the rectum:

(a) Rectopexy (posterior and lateral); (b) Colopexy; (c) Fixation of the pelvic colon to the anterior abdominal wall; (d) Fixation of the pelvic colon to the pelvis.

3. *Procedures of which it is the aim to efface the pouch of Douglas* (notably the method of Moscowitz):

Then the Author, in more than three detailed pages, give the results of the operation which has for its object the suspension of the rectum.

III. *Resection of the mucosa only* (Procedure of Delorme-Juvara).

Technique, advantages and inconveniences of the method are clearly set forth.

The last chapter deals with the choice of operation with special reference to the general condition of the patient and the local condition.

Cases where resection by the scalpel is the only traetment possible:

1. Irreducible collapse; 2. Strangulated rectum; 3. Strangulated hadrocele; 4. Extensive and deep ulceration of the rectum; 5. Stricture; 6. Invagination by malignant tumor.

Outside of these eventualities, resection should not be employed because of the immediate danger of hemorrhage and infection, especially of stricture, even after several months.

When the prolapse may be reduced without danger, three methods are especially recommended:

Colopexy of Quénu and Duval is the most nearly perfect and the least dangerous, to be completed, in case of need, by a posterior perineorrhaphy and by the silver wire encircling of the anus. If laparotomy is contraindicated is it necessary to limit oneself to a less shocking perineal operation and to employ the technique of Delorme-Juvara? If the physical or psychic state of the patient prohibits the use of this latter procedure, one may do the encircling of the anus with metal wire under local anesthesia.

The Author presents thirteen unpublished observations, 5 colopexies, 3 operations employing the Delorme-Juvara technique, 5 encircling of the anus. A detailed bibliography completes the work.

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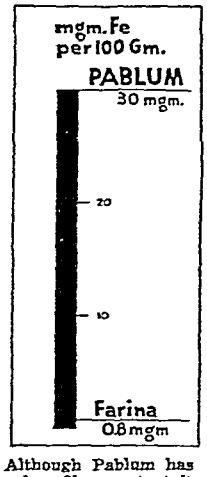


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SECTION I—*Clinical Medicine: Diseases of Digestion*

The Use of Chondroitin in Idiopathic Headache (Including Migraine)*

By

LATHAN A. CRANDALL, Jr., M.D., Ph.D.
GEORGE M. ROBERTS, M.S., M.D.
and
LOWELL D. SNORF, M.D.
CHICAGO, ILLINOIS

THE use of chondroitin (chondroitin sulphuric acid) in the treatment of idiopathic headache of the migraine type was made the subject of a preliminary report in 1933 (1). This study has been continued and extended to include data on 151 patients over a maximum period of 3 years. Our results warrant discussion on two grounds: first, the demonstration that chondroitin exhibits a definite physiologic action; second, the possibility that this substance may prove to be of therapeutic value in prevention of idiopathic headache, a field in which treatment is too frequently unsatisfactory.

Our interest in the action of the carbohydrate fractions (prosthetic groups) of the mucoproteins was aroused by the apparent systemic effect of mucin in certain experimental animals. Since such an action could hardly be attributed to the protein fraction of mucin, we attempted to prepare mucoitin (the prosthetic group of mucin). But mucoitin is difficult to prepare in quantity, whereas chondroitin (the very similar carbohydrate group of chondromucoid) can easily be made in large amounts. We therefore studied the action of chondroitin in patients with "peptic" ulcer, and found some evidence of beneficial action (2). Certain of these ulcer patients complained of headache of the migraine type, and the administration of chondroitin seemed to reduce the frequency and severity of the headache to a marked degree. We therefore continued with the study of chondroitin in uncomplicated idiopathic headache.

Chondroitin sulphuric acid is a definite chemical compound composed of 2 molecules of glucuronic acid, 2 molecules of galactosamine to which acetyl radicals are attached, and 2 sulphate groups. Its chemistry is discussed by Levene (3). In order to be able to prepare large amounts for administration to patients it was necessary to develop a simple method of preparation which avoided the use of barium or other toxic materials. The method used consists essentially of extracting cartilage with 2% sodium hydroxide, neutralizing the alkali, and precipitating with alcohol. Material so prepared contains a certain percentage of impurity. For approximately 1 year it was purified by precipitation with glacial acetic acid; more recently we have been using a product which contains approximately 25% of impurity (chiefly salts and protein)†. The clinical results with the less pure preparation are entirely comparable with those obtained with the purified product. The amount of chondroitin sulphuric acid present has been determined by analyzing for glucuronic acid (4). Sulphate analyses have indicated that the theoretical amount of sulphate radical is not present. The product therefore is actually a mixture of chondroitin sulphuric acid and chondroitin. We have preferred to use the latter term since it is equally descriptive.

THE USE OF CHONDROITIN IN IDIOPATHIC HEADACHE

We have purposely included in our series all available cases of headache which could not be ascribed to a known cause. Although a more or less definite syndrome termed migraine is generally recognized, we are totally ignorant of its etiology and it is impossible to say whether those headaches which do not present the classical features of migraine are nevertheless on the same basis, whether classical migraine forms a group by itself, or whether there may be more than one cause of migraine and that we may therefore be using this single term for more than one entity.

For purposes of study in this field it is highly desirable to set up rigid criteria, in so far as possible, in order that similar cases may be studied by various workers. We have therefore classified as migraine only those patients having: (1) Both a family history of periodic headache and a definite periodicity in the patient for a term of years; (2) Having at some time 2 of the following 3 characteristics: (a) aura (b) nausea and or vomiting (c) unilateral headache.

Others have noted the tendency for nausea and vomiting to play a predominant part in the picture when the attacks of migraine begin in childhood, and for these symptoms to become less and less prominent with advancing years. We have further noted, and have verified our observation by discussion with others, that as attacks of typical migraine become more and more frequent as the patient reaches middle life there is a tendency toward the development of frequent, perhaps daily, headache of a different character. A number of patients who have characteristic attacks of migraine

*From the Department of Physiology and Pharmacology, and the Department of Medicine, Northwestern University Medical School, Chicago, Illinois.
Submitted March 12, 1936.

†Supplied by courtesy of The Wilson Laboratories, Chicago, Illinois.

TABLE I

Cases of Classical Migraine

No.	Sex	Age	Age at Onset	Months Under Observation	Days Between Attacks		Severity of Attacks		Results *
					Before Chond.	During Chond.	Before	During	
1	M	38	18	2	8-12	7	Mod.	Mod.	O
3	F	49	35	27	7-10	10-26	Sev.	Sl.	F
4	F	30	15	34	7	Rare	Sev.	—	G
5	F	32	22	37	7-28	Rare	Sev.	—	G
6	F	18	14	4	14-21	Rare	Mod.	—	G
7	F	33	7	18	2-4	Rare	Sev.	—	G
8	F	41	13	32	14	Rare	Sev.	—	G
9	M	38	6	24	7-10	Rare	Sev.	—	G
11	F	49	34	18	7	Rare	Sev.	—	G
12	F	39	18	12	28	Rare	Sev.	—	G
13	M	10	5	4	14-28	45+	Sev.	Mod.	F
15	F	37	24	6	28	Rare	Sev.	—	G
17	F	25	15	20	7-12	40	Sev.	Sl.	F
18	F	30	10	4	7-14	7-20	Sev.	Sev.-Mod.	O
19	M	31	27	26	4-10	21-60	Sev.	Sev.-Sl.	F
24	M	11	8	6	7-30	Rare	Sev.	—	G
33	F	26	15	10	7-13	17-36	Mod	Mod.	F
34	M	42	15	3	7	7	Mod.	Mod.	O
35	F	41	16	9	14	28	Sev.	Mod.	F
39	F	44	25	14	12-18	Rare	Sev.	—	G
40	F	38	19	2	7	7	Sev.	Sev.	O
41	M	35	10	9	7-14	Rare	Mod.	—	G
42	M	52	37	2	1	1	Sev.	Sev.	O
44	F	28	24	4	28	Rare	Mod.	—	G
45	F	58	15	2	3-10	6-8	Mod.	Mod.	O
48	F	31	15	8	3-7	2-7	Sev.	Sev.	O
49	F	26	21	28	4-12	Rare	Sev.	—	G
51	F	34	14	22	28	Rare	Mod.	—	G
53	F	25	6	11	10-16	8-18	Mod.	Mod.	O
54	F	18	11	17	7	Rare	Mod	—	G
58	M	45	5	12	14	Rare	Sev.	—	G
59	F	31	8	17	7-28	Rare	Sev.	—	G
60	F	38	7	4	14-28	14-28	Sev.	Sev.	O
61	M	41	11	18	3-14	Rare	Sev.	—	G
63	F	26	21	4	2	2	Sev.	Sev.	O
64	M	52	42	2	1	1	Sev.	Sev.	O
65	F	40	12	30	7-14	26-36	Sev.	Mod.	F
68	F	44	22	28	21-28	50+	Sev.	Sl.	G
69	F	32	10	2	2-10	Rare	Sev.	—	G
75	F	39	34	2	7-14	7-14	Sev.	Sev.	O
76	M	24	18	6	2-7	4-12	Sev.	Mod.	F
77	F	33	25	9	7	25	Mod.	Sl	F

* G — satisfactory
F — fair
O — less than 50% improvement

occurring perhaps every 7 or 14 days also complain of less severe headaches, not preceded by an aura or accompanied by nausea or vomiting, which may be much more frequent to the point of being present constantly. Such atypical headache, occurring in patients with migraine, we have termed "interval headache" for purposes of description. In patients presenting typical attacks of migraine interspersed with atypical "interval" headaches, both types of headache have ordinarily improved to about the same degree whenever there has been a response to any form of treatment.

Patients with headache which does not fulfill all of the criteria for migraine but who have idiopathic headaches of the migraine type we have grouped under the classification "migrainoid." The majority of our cases are dispensary patients and in some instances

TABLE I (Cont.)

Cases of Classical Migraine

No.	Sex	Age	Age at Onset	Months Under Observation	Days Between Attacks		Severity of Attacks		Results*
					Before Chond.	During Chond.	Before	During	
81	F	44	26	6	28	28	Sev.	Sl	F
82	M	37	21	2	4-14	4-14	Mod.	Mod	O
88	F	31	24	22	28	Rare	Sev.	—	G
90	F	27	17	16	3	12	Sev.	Mod	F
91	M	61	12	6	7	21	Mod	Mod	F
93	F	33	17	23	10	Rare	Sev	—	G
94	M	40	12	4	3	3	Mod.	Mod	O
95	F	32	8	10	2-5	30—	Sev.	Mod.	F
96	F	30	12	6	2-5	10-25	Sev.	Sl-Sev	F
101	F	37	12	3	14-28	Rare	Sev.	—	G
102	M	37	7	6	10-14	10-14	Sev	Sev.	O
103	F	45	12	27	5-10	28+	Sev.	Sl	G
115	F	39	14	17	21-28	Rare	Sev.	—	G
120	F	41	35	14	3-6	Rare	Mod	—	G
121	F	35	3	2	3	14	Sev.	Sev.-Mod	F
122	F	40	36	26	1-8	Rare	Mod	—	G
127	M	52	7	10	6-10	Rare	Sev.	—	G
128	F	46	12	2	3-7	3-7	Sev.	Sev	O
130	M	35	13	4	2-7	6-9	Sev.	Sev	O
131	F	35	14	12	6-10	Rare	Sev	—	G
133	M	47	3	2	28	28	Sev	Sev	O
146	F	47	16	15	5-7	Rare	Sev	-	G
148	F	31	6	15	5-9	14+	Sev	Sl	F
150	F	38	16	34	2-14	Rare	Sev	—	G
151	F	39	15	3	7-35	7-35	Sev	Sev	O
160	F	40	28	16	3-6	Rare	Sev	—	G
161	F	27	12	14	7-21	Rare	Sev	—	G
163	F	38	16	4	11-14	11-14	Sev	Sl	F
165	F	36	8	10	2-5	28	Sev	Sev	F
166	F	44	13	18	7-21	Rare	Sev	—	G
169	F	36	12	9	6-12	7-60	Sev	Sev	O
173	F	40	15	12	5-8	28+	Sev	Mod	F
174	M	29	10	18	14	Rare	Sev	—	G
175	F	35	13	9	1	1-2	Sev	Mod	O
177	F	30	20	5	14	14	Sev	Mod	O
178	M	31	10	17	7-14	Rare	Sev	—	G
179	M	26	15	12	2-7	Rare	Sev	-	G
180	M	38	28	11	2-10	5-25	Sev	Sl-Mod	F
182	M	24	18	14	1-4	Rare	Mod	—	G
183	F	33	18	8	12-18	Rare	Sev	—	G
184	F	32	14	5	28	Rare	Sev	—	G

* G — satisfactory
F — fair
O — less than 50% improvement

information concerning the incidence of headache in the family is lacking, or there may be a positive family history and definite periodicity of the headache with nausea and vomiting but bilateral pain and no aura. Such cases might be presumed to be migraine, but they verge gradually into the type in which bears no resemblance to classical migraine. This last group, which we have termed "simple idiopathic headache" exhibits little more than head pain which may be constant or periodic. The chief merit of such a classification is to distinguish those patients who unquestionably exhibit the migraine syndrome, so that a comparison of our results with those of others is possible.

The treatment of idiopathic headache with the purified chondroitin first employed was carried out as previously described (1). The material used during the last 2 years must be given in somewhat larger dosage because it contains approximately 25% of inert

material. We begin routinely with 4 capsules (8 grains each) 3 times daily before meals and continue this dosage until some impression of the response of the patient is obtained. If after the first month or two the result is not satisfactory, the dosage may be increased to 18 or 24 capsules daily. Our experience indicates that the division of the daily dose into 3 parts taken before meals is not essential. It is essential that the patient take the full number daily. We have not suggested a reduction in dosage until a thoroughly satisfactory response has been maintained for a period of several months; the number taken daily may then be decreased in some instances although we have no cases in which fewer than 6 capsules daily are necessary to prevent the attacks.

Because of the well known tendency for patients with migraine to improve temporarily when placed on any new form of therapy a number of the patients who had responded satisfactorily to chondroitin were given similar capsules containing calcium lactate and were not informed of the change. Others were started on calcium lactate in this form and continued on such a placebo for 1 month. Not all patients who discontinue chondroitin have a prompt recurrence of attacks. Therefore the substitution of calcium lactate in those cases on treatment did not always result in exacerbations. Where the attacks did recur there was again a prompt improvement when chondroitin was again given. When 15 patients were given calcium lactate in capsules as their first medication, 8 reported marked improvement when chondroitin was substituted without their knowledge of the change. Another control of the psychogenic factor was unwittingly carried out when a change in the method of preparation of the chondroitin resulted in an inactive product. We were not aware that the new product was ineffective until the patients on treatment at the time reported recurrences; when given chondroitin made by the standard process these patients again reported satisfactory results.

Tables I, II, and III show the results obtained by the administration of chondroitin in cases of migraine, migrainoid headache, and simple idiopathic headache respectively. The patients were not selected, except that each was carefully examined to exclude possible known causes of headache. Of the patients exhibiting apparent benefit none are included who have been under treatment for less than 4 months. In those showing no improvement the administration of chondroitin was continued for at least 2 months, since the response in some cases is slow. Success of the treatment was estimated by the change in frequency and severity of the attacks. The headaches were graded *severe* if the patient was completely incapacitated, *moderate* if able to be up and around but not able to engage in ordinary activity, and slight if they were not troublesome.

It is interesting to note that between 45 and 50% of patients in each of the 3 groups obtained satisfactory relief from their attacks. This suggests that there may be no essential difference in the etiology of idiopathic headache whether it manifests itself as typical migraine or as simple headache without the characteristics of the migraine syndrome. We consider that satisfactory results have been attained when the patient has so few or such slight attacks that they are no longer a source of annoyance and would not lead him to consult a physician. Actually many of these individuals have had no attacks during the course of treatment. However, we have observed that patients who have progressed satisfactorily for 4 to 8 months without any headache may have an attack as the result of psychic trauma. Headache in such instances has followed the death of the husband, loss of the home by fire, loss of employment, marital difficulties, etc. After attacks so precipitated the patient will ordinarily be headache free for a further long period. Such cases are considered to have had as good a result as those who remain completely free from headache for long periods in the absence of any outstanding mental or physical upset. It is apparent that the administration of chondroitin acts to "increase the headache threshold," rather than to remove completely the underlying cause.

Patients in whom the response is classified as "fair" have reported at least a 50% reduction in frequency or severity; in case of question as to the percentage decrease they are termed not relieved. Patients with a "fair" result are often most grateful, since many of them have failed to obtain any benefit from other forms of treatment.

No untoward effects have been observed as a result of the continued administration of large amounts of chondroitin to patients or experimental animals, with the exception that some individuals may report an increase in flatulence which as a rule subsides within the second week. Where the flatulence is associated with an "irritable bowel" chondroitin in a few cases may produce enough distress to be troublesome. Complete elimination of starchy foods and uncooked fruit or vegetable from the diet will usually make it possible for these cases to remain symptom-free on chondroitin. Where such dietary measures have been introduced chondroitin has been discontinued and the effect of the diet alone has been ascertained. In some instances such a dietary regime produces improvement, but very rarely satisfactory relief.

A marked subjective sense of improvement has been reported by a number of individuals who previously complained of a constant sense of fatigue. Such a response is most difficult to evaluate and is only mentioned because so often spontaneously described by the patients. This increased sense of well-being usually accompanies relief of headache and may therefore be due to the absence of periodic incapacitation. However, it may be so striking as to suggest that it is not secondary to freedom from attacks, and is occasionally seen in patients that report only slight improvement in headache. It may be accompanied by an increase in appetite; a number of patients have gained weight.

When the daily administration of chondroitin is discontinued many patients remain headache-free for a considerable period of time. In fact, 2 have reported intervals of more than 9 months of freedom after taking chondroitin for only 4 weeks; these cases are not included in our series, since such an exceptional result leads us to suspect a psychogenic factor. In the majority of patients there is a recurrence of the typical symptoms within a few weeks after discontinuing the therapy. Some may have an attack if they omit their regular dosage for even 1 or 2 days. In a number of patients who have been on treatment for several months the attacks have not returned for 3 to

TABLE II

Cases Resembling Migraine But Not Fulfilling All Criteria (Migrenoid)

No	Sex	Age	Age at Onset	Months Under Observation	Days Between Attacks		Severity of Attacks		Result*
					Before Chond	During Chond	Before	During	
2	F	39	9	8	3-7	4-10	Sev	Sev	O
14	F	34	20	25	14-21	Rare	Sev	—	G
16	F	42	27	7	7-11	21	Sev	Sl-Mod	I
20	F	43	21	2	4-8	4-10	Sev	Sev	O
21	F	29	18	8	14-28	Rare	Mod	—	G
23	F	35	7	30	3-20	Rare	Mod	—	G
27	F	47	40	20	14	Rare	Mod	—	G
31	M	57	30	2	1	1	Mod	Mod	O
38	M	43	38	6	7	15	Sev	[illegible]	I
43	F	27	14	34	1-7	Rare	Sev	—	G
46	M	44	22	2	1-5	1-7	Mod	Mod	O
50	M	25	12	3	7	14	Mod	Mod	I
55	F	26	13	12	7	Rare	Sl	—	G
66	M	67	16	4	1	1	Sev	Sev	O
67	F	32	12	12	28	Rare	Mod	—	G
72	F	32	31	6	7-12	Rare	Mod	—	G
80	F	40	18	27	1-28	6	Sev	Sl-Mod	I
83	F	26	23	14	1-8	Rare	Mod	—	G
86	F	53	5	4	1-9	1-8	Mod	Mod	O
87	F	19	18	4	2	Rare	Mod		G
104	M	40	27	3	1-4	1-7	Sev	Sev	O
106	F	33	3	6	2-3	Rare	Sev	—	G
107	M	24	13	4	1-4	3	Mod	Mod	O
109	F	30	28	4	2-7	2-7	Sev	Sev	O
112	F	37	17	12	Rare	Rare	Sev	—	G
117	F	43	28	17	7-28	28	Sev	Sl-Mod	I
118	F	39	10	18	7-14	28	Sev	Sl	G
123	F	62	12	4	2-7	2-7	Sev	Sev	O
124	F	37	26	20	10-14	Rare	Mod	—	G
126	F	43	38	2	1-3	2-7	Sev	Sl	I
134	M	19	20	8	5-7	Rare	Sl	—	G
135	M	28	20	20	4-9	Rare	Mod	—	G
137	M	43	12	2	7	7	Sev	Mod	O
138	M	39	37	23	2-7	Rare	Mod	—	G
140	F	38	33	9	5-9	28	Mod	Mod	I
143	F	32	25	14	10-14	Rare	Mod		G
144	F	41	20	6	3-8	Rare	Sl		G
145	M	33	13	6	5-7	Rare	Mod	—	G
157	F	35	20	8	14-21	20-28	Sev	Sl-Mod	I
159	F	38	22	6	1-3	1-7	Sev	Mod-Sev	O
164	F	54	33	8	21-28	Rare	Sev	—	G
167	F	51	16	6	7-21	[illegible]	Sev	Mod-Sev	I
168	F	51	22	6	3-12	[illegible]	Sev	Sev	O
170	F	41	11	7	2-7	28	Sev	Mod	I
172	F	45	30	12	7-8	2	Sev	Mod	I
176	F	44	37	5	7-10	10-14	Sev	Sev	O
181	F	38	21	10	7-21	[illegible]	Mod	Sev	G

* G — satisfactory
I — fair
O — less than 50% improvement

TABLE III

Non-Migrainous Idiopathic Headache

No.	Sex	Age	Age at Onset	Months Under Observation	Days Between Attacks		Severity of Attacks		Results *
					Before Chond.	During Chond.	Before	During	
25	M	36	27	14	6-10	Rare	Sl.	—	G
26	M	45	43	4	1	Rare	Mod.	—	G
28	M	42	42	4	1-3	Rare	Sl.	—	G
29	F	14	8	10	2	26+	Mod.	Sl.	G
30	M	49	44	3	1	1	Mod.	Sl.	O
32	F	38	36	4	3-14	Rare	Mod.	—	G
73	F	54	30	4	10-14	10-14	Mod.	Mod.	O
74	F	42	40	5	3-7	21+	Mod.	Mod.	F
78	M	49	44	4	1	Rare	Sl.	—	G
79	M	31	12	2	1-14	1-14	Mod.	Mod.	O
105	M	39	39	8	1	Rare	Sl.	—	G
114	F	32	12	3	1	1	Mod.	Mod.	O
116	M	33	31	6	2	7	Mod.	Mod.	F
119	F	40	40	4	5-7	Rare	Sev.	—	G
125	M	35	7	4	6-14	Rare	Sev.	—	G
132	M	57	32	2	1	1	Sev.	Sev.	O
139	M	34	28	16	1-5	10-12	Mod.	Sl.	F
141	M	47	45	2	3-7	3-7	Sl.	Sl.	O
142	M	37	27	6	7-10	14+	Sl.	Sl.	F

* G — satisfactory
F — fair
O — less than 50% improvement

6 months after discontinuation, and have then been present in a mild form.

OTHER OBSERVATIONS ON MIGRAINE

In patients not relieved by chondroitin we have used various methods of treatment suggested by others. We have also employed certain laboratory procedures in the hope of finding some method of classifying these cases. Certain observations on such findings in the group presenting the classical symptoms of the migraine syndrome may be of interest.

Methods of treatment other than chondroitin have included diet, calcium lactate, "Emmenin," "Theelin," sodium thiosulphate, ergotamine, and pituitrin. Our dietary measures have been confined to prescribing a bland diet low in starch and containing a high proportion of cooked fruit and vegetable in cases with carbohydrate intolerance and flatulence. Occasional improvement results from such management but the result is rarely entirely satisfactory. Calcium lactate alone or in combination with diet has proven to be of little benefit. "Emmenin" and "Theelin" have been used where the attacks seemed to be related to the menstrual period; "Emmenin" has given good results in 2 out of 10 cases, "Theelin" in about the same proportion. Sodium thiosulphate given by intravenous injection in 1 gram doses twice weekly has usually failed when chondroitin has failed, but has further improved some patients who had obtained only a fair response with chondroitin. We have seen a number of patients who have previously been given ergotamine. These cases, as well as those in which we ourselves have used this alkaloid, have responded promptly to subcutaneous injection although administration by mouth has been of little benefit; similar results are reported by others. It should be pointed out that ergotamine may so greatly increase the nausea, even though the headache is abolished, that the patient refuses its use. Pituitrin, 0.5 c.c. subcutaneously given early in the attack, has caused a cessation of all symptoms in a number of cases.

Our laboratory determinations have been of no assistance in the classification of cases. In confirmation of previous reports, we find an elevated plasma cholesterol in approximately 50%; this finding is not as a rule present when the headache can be ascribed to known causes but is not sufficiently consistent in migraine to be of value. Serum calcium determinations in 25 patients with classical migraine have given only normal values. Beazell and Crandall (5) have found the purine bodies of the blood to be within normal limits both during the attacks and in intervals of freedom; they have also been unable to confirm (6) the reported decreased output of female sex hormone in the urine. Quantitation of the urinary sex hormone is so unsatisfactory at the present time that we question whether such studies can yield significant results. In some cases of migraine the basal metabolic rate tends to be low or at the lower limit of normal; this finding is perhaps even more common in idiopathic

TABLE IV

Summary of Results

	Satisfactory	Fair	Less than 50% Improvement
Migraine 83 patients	41 (49.4%)	20 (24.1%)	22 (26.5%)
Migrainoid 47 patients	23 (49%)	11 (23.4%)	13 (27.6%)
Non-migrainous 19 patients	9 (49.4%)	4 (21%)	6 (31.6%)

TABLE V

Age Distribution of Patients

	0-10	11-20	21-30	31-40	41-50	51-60	61-70
Migraine	1.2%	3.6%	20.5%	49.4%	19.3%	4.8%	1.2%
Migrainoid	0.0%	2.1%	17.0%	38.3%	27.6%	10.8%	4.2%
Non-Mig.	0.0%	5.3%	0.0%	52.6%	31.6%	10.5%	0.0%

headache not of the migraine type. Administration of thyroid in such cases has been of benefit.

MECHANISM OF ACTION OF CHONDROITIN

At present the most significant conclusion to be drawn from our results is: chondroitin produces a definite physiological effect on oral administration. Whether or not chondroitin proves sufficiently useful to be added to the list of agents which deserve trial in the individual case of idiopathic headache, the demonstration of its action in any percentage of cases opens a new field. No physiological action of chondroitin or any of its constituents has been demonstrated previously. Little is known of the metabolism of glucuronic acid in the body, less concerning glucosamine or galactosamine. We do not now have sufficient evidence on which to base a satisfactory theory which will explain the action of chondroitin, but certain studies which have been made may be recounted.

In order to determine whether chondroitin might cause improvement in migraine by altering conditions

TABLE VI

Sex Distribution of Patients

	Migraine	Migranoid	Non-migrainous
Males	29%	25.5%	68.5%
Females	71%	74.5%	31.5%

in the gastro-intestinal tract, its effect upon the bacterial flora of the stool and upon the secretion of bile have been studied. As stated in our preliminary report (1), Crandall and Lederer found no change in fecal flora when large doses of chondroitin were administered to normal individuals. Stinchfield and Crandall (7), using bile fistula dogs, found no change in biliary output following oral administration of chondroitin although the general condition of the animals seemed to be improved.

Further evidence of systemic action has been obtained from a study of the effect of mucin and chondroitin in Eck fistula dogs by Crandall, Roberts, and Gibbs (8), who reported weight gains and improved general nutrition in these animals which ordinarily maintain their weight at about 25% of the preoperative level. Gibbs and Crandall (9) have further studied the protective action of chondroitin when given to dogs together with cinchophen. Animals receiving 100 mgm. cinchophen per kilo per day ordinarily die in 1 to 3 weeks with evidence of marked liver damage and acute gastric or duodenal ulcers. When chondroitin is added to the diet of such animals the length of life is approximately doubled and the ulcerative processes become much more chronic.

It has long been known that certain toxic substances are excreted in the urine in combination with glucuronic acid. The body manufacturers this substance, presumably in the liver. It is not known whether a deficiency of glucuronic acid ever occurs. The evidence thus far, however, suggests that the liver is concerned in whatever metabolic changes are brought about by the administration of chondroitin. Since we have given other products which contain glucuronic acid but no glucosamine or galactosamine and have obtained some benefit in idiopathic headache (1), it appears more probable that the glucuronic acid fraction of chondroitin is active than that the effectiveness of chondroitin is due to its amino-sugar content.

SUMMARY

Since the publication of a preliminary report on the use of chondroitin (chondroitin sulphuric acid) in 42 cases of idiopathic headache, a continuation of the study has made possible the compilation of data on more than 150 cases. The longest period of observation has been 3 years. Patients who showed no improvement have been observed for at least 2 months, those who reported benefit have been followed for 4 or more months.

Chondroitin (obtained from cartilage) contains glucuronic acid, glucosamine, and sulphate radicals. The material used has been a commercial extract approximately 75% pure.

The majority of cases treated have been of the migraine type. In approximately 50% of all instances

TABLE VII

Correlation of Response in Migraine with Age, Sex, and Frequency of Attacks

	Age		Sex	
	Over 35 (35 patients)	Under 35 (47 patients)	Males	Females
Satisfactory	57%	40.5%	41.6%	52.5%
Fair	29.6%	23.4%	20.8%	25.4%
Less than 50% improvement	14.4%	36.1%	37.6%	22.1%

	Frequency	
	Average interval between attacks 10 days or less (51 patients)	Average interval between attacks more than 10 days (32 patients)
Satisfactory	41.0%	65.6%
Fair	29.5%	15.7%
Less than 50% improvement	29.5%	18.7%

the results have been satisfactory; i.e., headache, when it persisted, was not severe enough to be troublesome. In another 20% the frequency or severity of the attacks was reduced at least 50%.

Whether chondroitin will be found useful by the medical profession in the treatment of idiopathic headache can only be determined by the test of time. A point of immediate interest is the demonstration of the physiological effect of this complex carbohydrate, concerning which so little is known. The possible mechanisms of its action are discussed.

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The Gastro-Intestinal Symptoms in Hypertension*

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IN a clinic where a large number of gastro-intestinal patients is seen, one cannot help but be impressed with the number who also have hypertension. The question arises whether these digestive complaints are not in some way related to the hypertension and its concomitant cardiovascular or neurogenic phenomena, or whether they are purely accidental and unrelated. It is recognized that hypertension is associated with nervous instability (1-2), vasomotor disturbances (2), migraine (2), colitis (2) and hyperthyroidism (3-4-5-6-7-8-9). It is also recognized that some of these conditions may give rise to gastro-intestinal symptoms (10-11).

The present report consists of a study of 60 consecutive hypertensive patients whose systolic blood pressure reached 160 m.m. of Hg, or the diastolic 95 m.m., or in whom a hypertensive heart was found at autopsy. Fifty-one of these patients had digestive complaints during life; the other nine had some alimentary tract lesion of importance which was discovered at operation or at autopsy.

There were 25 males and 35 females, the *age* grouping was as follows:

Third decade 4, Fourth decade 9, Fifth decade 15, Sixth decade 12, Seventh decade 17, Eighth decade 2, Unknown 1.

The most frequent symptoms and signs were: epigastric pain or distress 23, constipation 18, abdominal pain 16, belching 13, nausea and vomiting 11, melena 7, jaundice 5, right upper quadrant pain 5, diarrhea 4, anorexia 4, pressure against the heart 3, "indigestion" 2, right lower quadrant pain 2, fullness in epigastrium 2, weight in the stomach 1, left lower quadrant pain 1, and a cold feeling in the epigastrium 1. It was found on dividing these symptoms according to sex that the females complained more frequently of belching, constipation, and abdominal pain whereas the males complained more of epigastric pain.

A classification of the *diagnoses* which occurred two or more times was made. This divided the cases into two main groups, chronic and acute, with subgroups as shown in Table I. It was found that 85 per cent of all the 60 cases could be included in this classification.

TABLE I

Chronic		
1.	Peptic Ulcer (Hyperthyroidism 3)	10
	Ulcer like pain	4
2.	Colitis (Hyperthyroidism 4)	9
	Diverticulitis	1
	Melena	1
3.	Gastrocardiac Syndrome	9
4.	Gall Bladder Disease	5
5.	Constipation (Hyperthyroidism 4)	4
6.	Gastric Neurosis (Magen neurose)	3
Acute		
1.	Uremia Syndrome	6
2.	Hemorrhage:	
	In stomach	3
	In pancreas	1
3.	Coronary occlusion	2
4.	Perforated Peptic Ulcer	2

THE CHRONIC AFFECTIONS

Ulcer: There were 10 cases, including 2 perforated, with a definite diagnosis of ulcer by X-ray examination or at autopsy. Two of the cases of gastric hemorrhage were most probably due to ulcer, since cancer and cirrhosis of the liver, the two other most common causes of gastric hemorrhage, could be excluded by the long course of the disease and the physical findings. This would give a total of 12 ulcer cases, an incidence of 20%. Among the males there were 8 cases; and since there were 25 males, the incidence was 32 per cent. There were four other cases with

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pain quite characteristic of ulcer, but in whom the X-ray pictures were either negative or not taken.

Colitis: Under colitis were included 9 cases. These patients had such symptoms as belching, constipation, or diarrhea or both, melena, abdominal pain, and mucus in the stools. Often they showed also a spastic colon when X-rayed. As sub-groups of colitis there was one case of diverticulitis and one case of melena, which probably represented some form of colitis. Constipation was the sole complaint in 4 cases, otherwise when it occurred it was not the outstanding symptom and was usually associated with colitis.

Gastrocardiac Syndrome: There were nine cases listed under gastrocardiac syndrome. In this condition, the epigastric pain was usually found dependent upon or closely associated with symptoms of a weakened myocardium. Although this syndrome has been recognized for a long time and its significance properly interpreted, still, every once in a while, it is mistaken for gall bladder disease. Attention should therefore be called to it because it may frequently be relieved by small doses of digitalis. The distress was always in the upper abdomen and radiated upward to the sternum, chest or left arm. The distress was brought on or aggravated by exertion. Complaints such as shortness of breath or other complaints pointing to a weakened myocardium were common. Flatulence with eructations of gas was also a very frequent complaint. The primary cause for this condition is not clear, but the relief obtained from digitalis points to the cardiac condition as primary. However, Roemheld thinks that these symptoms are caused by distention of the stomach, by elevation of the left leaf of the diaphram, which is more mobile than the right, and also by reflex caused by toxic products of digestion. The following cases are representative of this group:

Case I: A female, 68 years of age, complained of gastric distress, nausea, and constipation. There was no actual pain and the distress was not related to meals. She also complained of weakness, loss of weight, and shortness of breath.

On examination, the lips were cyanotic; there was a systolic murmur at the apex and edema of the ankles. The blood-pressure was 170/90. X-ray examination of the stomach and duodenum was negative. The gall bladder showed faint concentration of the dye but no stones. The stools contained no blood or mucus. On small amounts of digitalis her dyspeptic symptoms disappeared. Comment: The cardiac picture is so prominent in this case that it is reasonable to believe that the gastric distress and nausea are in some way related to it, and the response to digitalis substantiates this belief.

Case II: A colored female, 48, complained of "misery" in the epigastrium radiating under the sternum, also dyspnea. She stated that gas accumulated in her stomach, pressed against her heart and made her heart beat fast. The heart was enlarged and the sounds were feeble with a systolic murmur at the apex. The blood pressure was 174/94. On small doses of digitalis, the alimentary tract symptoms were relieved.

Gall Bladder Disease: There were 5 cases included under the heading of gall bladder disease; of these, two had typical colic and stones were demonstrated in the gall bladder. In the remaining 3 cases, gall stones were found at autopsy; but it could not be said with certainty that the stones were the cause of the gastro-intestinal complaints, since the symptoms were atypical for gall bladder disease.

Gastric Neurosis: The diagnosis of gastric neurosis was made three times. The tendency is to use this as a last resort diagnosis when no organic lesion can be found in the abdomen. However, Dorfler (12) has described a rather definite group of digestive symptoms, to which he applied the term 'magen neurose'; the description was found to fit 3 cases in this series very well. The syndrome is characterized by pain in the epigastrium which is worse at night but better in the morning. Nourishment eases the pain. There is very little if any vomiting, but belching is common and is followed by relief. The bowels are regular or there may be alternate constipation and diarrhea. The patient usually has no difficulty in eating such foods as cabbage, radishes, carrots, etc. On palpating the abdomen, there is tenderness at every point of pressure. The patient is usually a blooming, well nourished person who also complains of other nervous symptoms such as palpitation, sleeplessness, cold feet, blood rushing to the head, headache, etc.

THE ACUTE SYMPTOMS

The acute symptoms were of a sudden onset, severe, often violent and associated with hemorrhage or rupture of a viscus. The first of this group comprised six cases called 'uremia syndrome' for want of a better name. The symptoms are ushered in with severe nausea and vomiting, with or without abdominal pain. The CO_2 combining power of the blood and the N.P.N. are usually elevated, and the blood chlorides may be reduced. There is headache; the patient becomes drowsy, then comatose; the disease runs a rapid downhill course and *exitus* is from what appears to be uremia. In some instances, however, the renal symptoms are in the background; and just before death, the cerebral manifestations are most evident. Two cases are cited:

Case I: A male, 66, was brought to the hospital because of continuous vomiting for 3 days, which he thought came on after eating canned apples. There were also abdominal pain, constipation, rigidity of the abdomen with signs of intestinal obstruction. The temperature was 101° and the B.P. 198/130. He improved and the signs of obstruction cleared up. Several days later, before he left the hospital, he became drowsy, irrational, dyspneic, the N.P.N. rose to 120 mg. per cent and he died in uremia.

Comment: The canned apples may have had nothing to do with these symptoms, and this represents an acute episode that can occur in the course of hypertension. However, even if the apples were the exciting cause, such a severe clinical picture is uncommon. Apples do not usually cause severe poisoning; and if botulism can be excluded, as it can in this case, recovery is the rule. The fact that the symptoms were so severe and terminated fatally shows an extreme degree of sensitivity in this patient.

Case II: A male, 58, was brought to the hospital because of sudden severe nausea and vomiting and coughing which had lasted a week. Up until this illness he had always been well. His temperature was normal and the blood pressure 210/150. The urine showed large amounts of albumin and at no time did his temperature exceed 99.6°. Edema and effusion in the pleural cavities developed rapidly, followed by anuria. He became restless and died

the next day, eight days after the onset of the nausea and vomiting.

Some of these cases do not terminate in uremia and the N.P.N. may remain normal, as a matter of fact the uremia, *per se*, may only be a terminal or incidental finding of some more general disturbance. Eppinger, *et al* (13) have described a similar syndrome which occurs after the ingestion of spoiled meat. There are nausea, vomiting and collapse, with signs of peritonitis. The temperature is usually low but may be elevated, the urine shows albumin, urobilin, acetone, indican and casts. At autopsy, the stomach mucosa is thickened, dark, with small erosions and ulcerations. They are more pronounced in the duodenum and large colon. The liver shows the typical picture of 'serous inflammation' as described by Rössle. The other parenchymatous organs are large and water-logged. Bordcley (14) has shown that a similar clinical syndrome terminating in uremia can occur after blood transfusion. The uremia following in the wake of severe burns when the partially decomposed skin proteins gain access to the blood stream is well known. It is possible that the 'uremia syndrome' herein described is similar to those described by Eppinger *et al* and Bordley and that a reaction of an allergic nature may be at the bottom of this syndrome. Persons with hypertension would probably be more subject to such manifestations than are normal persons since, as was previously shown, they are liable to have ulcers and other lesions in the alimentary canal which would allow partially split proteins and other toxic products of digestion to gain ready access to the blood stream.

Gastric Hemorrhage: Gastric hemorrhage occurred three times. Two of these patients complained of epigastric distress and one of these had a peptic ulcer. The third had no symptoms other than the hemorrhage. Perforated peptic ulcer occurred twice and hemorrhage into the pancreas occurred once.

Miscellaneous Cases: There were seven miscellaneous cases; the liver was the seat of the disease in four of these. Parenchymatous degeneration of the liver, carcinoma of the liver, cholangitis with liver abscess, and alcoholic fatty cirrhosis were observed once each. Intestinal tuberculosis occurred once; and gangrene of the ileum was observed once, at autopsy. The last case was one of recurring abdominal pains; these pains occurred several times a day, usually after meals.

Hyperthyroidism: It is significant that a large number of these patients showed some signs of hyperthyroidism, no less than eleven patients showing such symptoms. Among these, the diagnoses of colitis and ulcer were most frequent, occurring 4 and 3 times respectively. Constipation also occurred 5 times and diarrhea once. Because of this overlapping, hyperthyroidism was not included as a special heading in the table. There were 7 females and 4 males and all but two were over 40 years of age, five occurring in the sixth decade. The B.M.R. was done in all cases but one and ranged from 1.4 plus to 50 plus.

DISCUSSION

The high incidence of peptic ulcer in this series deserves some comment. According to Cabot (15) in approximately 16,000 patients, both with hypertension and normal blood pressure, who presented themselves with abdominal complaints, the incidence of peptic ulcer was 9.3 per cent. In this series, the incidence was 20 per cent which suggests that there may be more than an accidental relation between peptic ulcer and hypertension. Kylin (1) is of the belief that peptic ulcer is common in hypertension. He states that as the K/Ca ratio in the blood rises, such diseases as nervous disorders, hypertension, and ulcer become more frequent. Kylin (2) also states that the hypertensive patient is likely to have diabetes, asthma, gout, vasomotor disturbances, colitis, and migraine. Wechsler (16) in a very illuminating article on abdominal pain as a symptom of disease of the brain, quotes Cushing's series of 9 cases of interbrain lesions with peptic ulcer, two of which also had malignant hypertension.

Of considerable importance is the fact that cancer was a rare lesion in this series. Cancer of the stomach was not observed at all; and cancer of the bowel was seen one time, an incidence of 1.7 per cent. According to Cabot's figures, the incidence should have been 6 and 3.9 per cent respectively.

Colitis occurred 9 times, an incidence of 15 per cent; this is high also. Cabot does not even list colitis in his series.

It is of interest that the abdominal pains so frequently seen in tuberculosis were observed only once in this series. In Cabot's series, they were second on the list with an incidence of 12 per cent. Evidently hypertension, so rare in tuberculosis, serves to exclude that disease.

The fact that about 85 per cent of all the cases in this series fall into the simple classification given in the Table should be of help in the differential diagnosis of abdominal symptoms, if hypertension is present. If the symptoms are of a chronic nature, ulcer and colitis should be first considered; these two conditions made up about 50 per cent of all the chronic cases. The gastrocardiac syndrome should be easy to recognize; and if all of these are absent, then a careful investigation of the gall bladder should be made. If the symptoms are acute then we should think of the uremia syndrome, perforated peptic ulcer, gastric hemorrhage, or some similar vascular accident. Severe vomiting, weakness, headache, and sleepiness in a person with hypertension should direct attention to an impending uremia.

The association of the three conditions, *i.e.* hypertension, hyperthyroidism, and a lesion in the alimentary canal, such as colitis or ulcer, was seen seven times which suggests that there must be some relation between them. A nervous or circulatory disturbance of some kind is probably behind this triad; it may be of the nature of a neuro-vegetative imbalance. A discussion of this highly theoretical subject is beyond the scope of this paper.

SUMMARY

1. In the 60 cases of hypertension also having gastro-intestinal complaints, peptic ulcer occurred 12 times, an incidence of 20 per cent. This high incidence suggests a possible relation, but the series is too small to draw any definite conclusion.

2. Colitis was also frequent, it occurred 9 times, an incidence of 15 per cent.

3. Hypertension, hyperthyroidism, and a lesion in the alimentary tract such as colitis or ulcer occurred together 7 times. This strongly suggests that the concurrence of these three conditions is not accidental but that they are related and that some general disturbance of a circulatory or nervous nature is responsible for this triad.

CONCLUSION

It is reasonable to conclude that the gastro-intestinal symptoms seen with hypertension are to a considerable extent conditioned by the cardiovascular, neurovegetative, and other phenomena concomitant with the hypertension.

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Tobacco Sensitivity in Peptic Ulcer*

A Second Report

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IT has been a clinical impression among the workers in the Subclinic of this Clinic that patients affected with peptic ulcer do not respond to the routine ambulant treatment if they continue to smoke tobacco. For the last nine years it has been the custom in the Clinic to advise such patients against smoking.

Our experience in accordance with that of other observers, so much so that tobacco smoking has even been thought to have a part in the pathogenesis of ulcer (1, 2, 3, 4). There has been reason to think that tobacco smoking raised gastric acidity (3, 5, 6), and affected gastro-duodenal motility (7, 8). It might be suspected that the action of the tobacco was through the effects of nicotine (9, 10, 11, 12) on the autonomic system (13) by means of secretory and motility phenomena (14, 9).

In 1932, Harkavy, Hebald and Siebert (15) reported that intradermal injections of extracts of Burley, Virginia and Xanthis tobacco showed patient sensitivity to one or more of the extracts in 83% of a series of 68 cases of thrombo-angiitis obliterans. In 1933, Harkavy (16) gave his results of similar tests of cases of disease of the blood vessels and 281 controls. Among the latter he found that of 60 cases of gastro-duodenal ulcer, 16 cases, (26%) were sensitive to tobacco. Eleven of these had either a personal or family history of allergy. At the time of Harkavy's 1933 report, Sulzberger (17) gave confirmatory results from vaccination of patients with thrombo-angiitis obliterans. He found that in 95 cases of a hospital population including both male and female smokers, but excluding thrombo-angiitis obliterations patients and non-smokers, 36 % gave positive skin reactions to tobacco. Fifty-eight non-smokers were positive in only 16% of the cases. In 1934, Sulzberger (18), using denicotinized extracts and a solution of 0.4% nicotine, obtained, with ten nicotinless extracts, positive wheals in 78% of a series of thrombo-angiitis obliterans patients and in 36% of 95 controls. The nicotine injections Sulzbreger finds surprisingly inactive and innocuous. A group of cases reacting with wheal formation was investigated for passive transference and found all negative but one. Therefore, he concludes that the sensitization found is non-atopic and without re-agins. Sulzberger believes that an organ or part of an organ may be sensitized and that all allergens have favorite foci of sensitization. His test of sensitization is the production of the urticarial wheal.

In a previous communication (19), the authors reported the results of a study of sensitivity to intradermal injection of tobacco extract in a series of patients affected with peptic ulcer.

Two extracts of tobacco were used, one supplied by Dr. Coca and one prepared by Coca's method, of a combination of many tobaccos obtained at a tobacco shop. Fifty-five ambulatory patients with roentgen diagnoses of peptic ulcer were tested with Coca extract diluted 1:10 and with the extract of the combination of tobaccos, without dilution and diluted 1:10. Two of these patients gave characteristic positive reactions to the three preparations. Passive transfer was negative in each case.

After the completion of the above work it was pointed out that this method was faulty in that the extract had not been used in concentrated forms as in Sulzberger's study of thromboangitis obliterans. Ac-

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cordingly a new series of patients has been studied with the use of a concentrated extract.

METHOD

A tuberculin syringe was used to inject 0.02 c.c. of the concentrated extract intracutaneously into the outer aspect of the arm. This was followed immediately by a similar amount of diluting fluid near the first injection, as a control. The patient was kept under observation for one hour. The greatest reaction during that period was recorded.

Reactions were considered positive only if the following three conditions were found: (1) the wheal must be larger than the control wheal; (2) it must be surrounded by a definite zone of erythema; (3) it must show unmistakable pseudopod formation. In positive cases, passive transference by the method of Prausnitz (20) and Küstner was done. Control injection was made in the other arm in these cases.

MATERIAL STUDIED

Forty-four male patients with roentgen diagnoses of peptic ulcer, all smokers of tobacco were given these supplementary tests with concentrated tobacco extract.

RESULTS

Four of the forty-four patients gave marked characteristic positive reactions to the concentrated extract. Passive transfer was attempted from each of the four cases to four different individuals. Such was negative in the sixteen instances.

SUMMARY AND CONCLUSIONS

A former report is quoted where fifty-five peptic ulcer patients given intradermal injections of tobacco protein gave no evidence of sensitivity to tobacco protein. A criticism of this work is noted, namely that one of the two tobacco preparations was only used in dilution 1:10 and not in concentrated form. Forty-four more similar patients are reported, injected with the concentrated extract. Four of these gave positive local reactions. In every instance passive transfer was negative.

It is concluded from these combined results that it cannot be proved that sensitivity to tobacco protein plays any part in the pathogenesis of peptic ulcer since in no case was it possible to demonstrate re-agins and in neither series were wheals obtained in any significant proportions.

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Mesenteric Thrombosis

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WE deem it worth while to call attention to this small series of cases of mesenteric thrombosis because, contrary to our former conception of the condition, the diagnosis is easily made if it is borne in mind.

The most common combination of pre-existing findings were advanced age, marked arteriosclerosis, auricular fibrillation and left ventricular failure. When an individual with these manifestations suddenly develops abdominal pain, which at first is intermittent in character and which may be localized anywhere in the abdomen and shows no tendency to subside, one should consider mesenteric thrombosis. If, in addition, stool is passed and contains blood the diagnosis practically is complete. If the bowel is not evacuated spontaneously, and one is considering the possibility of a mesenteric thrombosis, it is well to look into the bowel and see if there is bloody stool present and not wait for a spontaneous evacuation. Practically all of the instances of mesenteric thrombosis were accom-

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panied by varying degrees of shock, fall in blood pressure and leucocytosis.

The literature on this subject which is in the English language for the last ten years is sparse; many of the cases reported were not proved by autopsy. In our four cases which were substantiated by autopsy, the diagnosis of probable mesenteric thrombosis had been made when the patients were first seen by us. Two of the cases, however, refused operation, one was *in extremis* and an operation could not be undertaken, one patient was operated upon and an extensive resection of the small bowel was performed.

CASE REPORTS

Case 1. Patient was a 69 year old, white female who complained of generalized abdominal pain which had started three days prior to hospital admission The patient had been known to have hypertension for many years. During her present illness, the abdominal pain was accompanied by nausea, vomiting and constipation On the

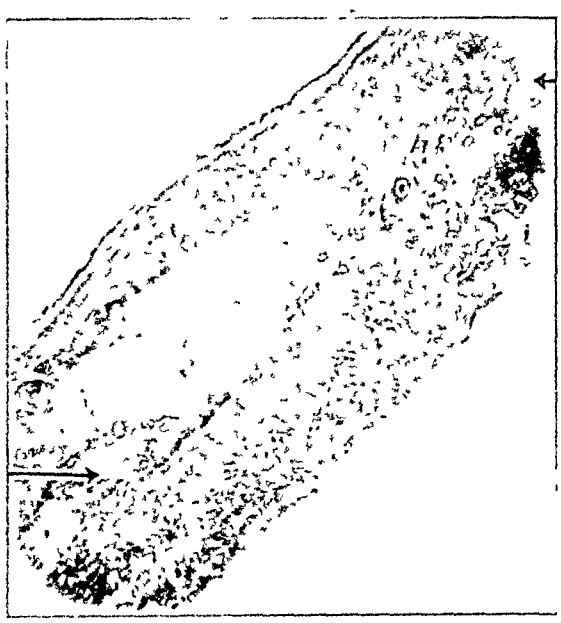


Fig. 1. Early gangrene (small intestine). Section of small bowel exhibiting infarction (Case 1).

day of admission, the patient had three bowel movements, each containing gross blood.

The *physical examination* revealed a dehydrated, senile female in shock. A slight amount of nodular thyroid tissue was palpable. Moist rales could be heard over both lung bases. The auricles were fibrillating at a rapid rate. The abdomen was rigid, tender mostly on the right side with evidence of peritoneal irritation. A *diagnosis* of probable mesenteric thrombosis was made. Operation was refused. The progress was rapidly downhill and the patient expired shortly after admission.

The *necropsy* revealed mesenteric thrombosis with infarction of the jejunum and ileum (Fig. 1).

Case 2. Patient was a 70 year old, white male, complaining of pain in the umbilical region. He had been under care for arteriosclerotic cardio-vascular disease for eight years and gave a history suggestive of a previous cerebral thrombosis He also had symptoms referable to vascular disease of the extremities.

Twenty-four hours prior to admission the patient experienced a cramp-like pain in the umbilical region; this was accompanied by shortness of breath and a feeling of weakness. He became markedly nauseated but did not



Fig. 2 Thrombosis of the superior mesenteric artery. (Case 2).

vomit. The pain migrated to the right lower abdominal quadrant No stool could be obtained.

Physical examination revealed a poorly nourished, white, elderly male He was in a state of severe shock There were many moist rales at both lung bases. A pleuropericardial friction rub was heard over the apex of the heart The abdomen was markedly distended and tender The tenderness was most severe in the epigastrium and lower quadrants. There was generalized abdominal muscle spasm The patient vomited large quantities of dark brown fluid

A diagnosis of probable mesenteric thrombosis was made but the patient's condition precluded operative intervention. He expired The autopsy revealed thrombosis of the superior mesenteric artery with infarction and gangrene of the small bowel (Fig 2).



Fig. 3. Thrombosis of the mesenteric artery. (Case 3).

TABLE I

Summary of Clinical and Laboratory Observations in Four Instances of Mesenteric Thrombosis

	CASE I	CASE II	CASE III	CASE IV
Age	69 years	70 years	76 years	76 years
Duration of complaint on admission	72 hours	24 hours	72 hours	Developed while in the hospital
Previous thrombosis or embolism elsewhere	None	Probable thrombosis. Cerebral artery 5 years previously	None	None
Manifestations of previous cardiovascular damage	Hypertension Auricular fibrillation	Dyspnea for 8 years. Transient numbness left side of body and left extremities 5 years ago — alternate pallor and cyanosis of toes	Thyroid adenoma	Hypertension; Auricular fibrillation
Outstanding features of present illness	Generalized abdominal pain —nausea — pain became more severe. No B.M. for 3 days. On day of admission had 3 B.M. without catharsis	Cramping pain in umbilical region—dyspnea, weakness—sudden nausea and vomiting —pain concentrated in right lower quadrant and became worse	Pain radiating across lower abdomen — distension — constipation—nausea and vomiting — Pain increased in severity. Bloody stool obtained by enema; lethargy	Sudden, lancinating pain in lower abdomen accompanied by nausea, vomiting and passage of bloody stool
Appearance	Emaciated — irrational. Actually ill — complains of severe pain—in shock	Poorly nourished — Acutely ill — in shock — vomited large quantities of dark brown bloody fluid	Undernourished — semi-stuporous—in shock after surgery —stupor deepened into coma and shock increased	Poorly nourished—in shock—slight dyspnea
Presence of heart failure	Left ventricular failure	Left ventricular failure	Left ventricular failure	Left ventricular failure
Condition of blood vessels	Marked peripheral sclerosis —Dorsalis pedis arteries not palpable. Varicosities of lower extremities	Large vessels were sclerotic and tortuous—Dorsalis pedis arteries not palpable—varices of lower extremities	Marked sclerosis of peripheral vessels—dorsalis pedis arteries not palpable	Marked sclerosis of peripheral vessels—dorsalis pedis arteries not palpable
Findings by examination of the abdomen	Generalized spasm — rigidity on right side—tenderness and rebound tenderness	Markedly distended with diffuse tenderness most in epigastrium and lower quadrants—marked muscle spasm	Distended — marked muscle spasm most severe in umbilical region	Rigid — distended — diffusely tender but most severe in lower abdomen
Blood in stool Constipation or diarrhea Duration of condition when first seen	Yes Constipated 65 hours	Blood looked for but no stool obtained Constipated 11 hours	Yes Constipated 36 hours	Yes Constipated 6 hours
Result	Expired	Expired	Expired after laparotomy	Expired after laparotomy
Laboratory findings	Urine— Albumin + loaded with W.B.C. occasional cast Blood— W.B.C. 23,500 R.B.C. 4,250,000 Hgb. 70% T Chem—N.P.N.—40	Urine— Albumin + Casts + W.B.C. + R.B.C.+ Blood— R.B.C. 6,500,000, W.B.C. 20,350, Hgb. 90% S. Chemistry—normal	X-ray abdomen; air distended loops of bowel arranged in layers Urine— Albumin + W.B.C. — occasional Blood— W.B.C.—20,000	Urine— Albumin + W.B.C. — Blood count—record lost
Autopsy findings	Mesenteric thrombosis—Infarction of jejunum and ileum — Chronic cholecystitis — Cholelithiasis — Chronic appendicitis and peri-appendicitis — Serosanguinous peritonitis	Arterial and arterioler sclerosis Myomalacia of heart — Adhesive pericarditis — Mural thrombosis of left ventricle — Thrombosis of superior mesenteric artery with infarction and gangrene of small bowel — Hemoperitoneum — Embolism left iliac artery — Bilateral renal infarcts — Encephalomalacia—Passive congestion of both lung bases	No autopsy but findings at operation as follows: Sero —sanguinous peritonitis — gangrene of jejunum and part of ileum thrombosis of superior mesenteric artery	Considerable athero — sclerosis —ulceration and thrombosis of upper part of thoracic aorta — rheumatic scars in myocardium—old infarct in kidneys — thrombosis of mesenteric artery — acute gastritis—central necrosis of liver — paralytic jejunum — pulmonary edema — adenomatous goitre — chronic cholecystitis with stones—infarction of small bowel
Blood pressure	130/90	100/80	90/60	100/50 after operation 30/0?
Pulse	144 (apex) 120 (radial) aricular fibrillation	120	Auricular fibrillation	120 (auricular fibrillation)
Temperature (rectal)	99° F.—rising steadily to 105° F.	99°-101° F.	99° F.	99°—100° F.

Case 3. Patient, a 76 year old, white, female, was under the care of Dr. L. J. Markus. She had experienced lancinating pains across the lower abdomen for about 72 hours before she was seen in consultation by one of us (S.S.B.). The patient had had a subtotal thyroidectomy 25 years previously for thyroid toxicosis.

The present illness was initiated with abdominal pains and later constipation. Nausea and vomiting appeared soon after the onset. The pain increased in severity and became localized to the umbilical region where it remained. Stool obtained by enema was grossly bloody.

Physical examination revealed an undernourished white senile female in shock. A small thyroid adenoma was palpable. There were a few moist rales over the right lung base. The auricles were fibrillating at a rapid rate. The abdomen was distended and rigid. Direct and rebound tenderness was most marked in the umbilical area.

A diagnosis of probable mesenteric thrombosis was made. The patient was immediately operated upon under local anesthesia and part of the jejunum and the entire ileum which showed infarction were removed; a jejunostomy was performed. The patient did not rally from the shock but expired a few hours later. The operation also revealed a serosanguinous peritonitis, gangrene of a part of the jejunum and the ileum and thrombosis of the superior mesenteric artery (Fig. 3).

Case 4. Patient was a white male, aged 76, complaining of generalized pain in the abdomen. He was under care for arteriosclerotic cardio-vascular disease.

The present illness developed while the patient was in the hospital for an unrelated condition. He suddenly experienced lancinating pain in the lower abdomen accompanied by nausea, vomiting and the passage of bloody stools.

Physical examination revealed a senile, white male in shock. A few moist rales were audible over both lung bases. The abdomen was rigid, distended and diffusely tender.

A diagnosis of mesenteric thrombosis was made and immediate operation was advised. The patient, however,

refused surgical intervention. He became rapidly worse and expired in a few hours.

Autopsy revealed thrombosis of the mesenteric artery and a paralytic jejunum.

SUMMARY

These four proven cases of mesenteric thrombosis exhibited almost identical major manifestations.

In most instances of this acute complication of advanced arteriosclerosis the diagnosis or at least the suspected diagnosis of this condition can be made when the patient is first seen if the condition is borne in mind.

In this series of four cases the diagnosis was made at the first contact but unfortunately the condition had been present in one patient for 6 hours, in another 11 hours, another 65 hours and another for 70 hours. All of the patients were in shock.

Heretofore, as cases generally are recorded in the literature also undue delay has occurred between the time the diagnosis was made and the surgical intervention. In spite of the advanced age of these patients, early diagnosis and early surgical intervention may be life-saving.

The ultimate *prognosis* of acute mesenteric thrombosis practically is hopeless. The underlying factors themselves fundamentally are serious, and the added shock of the thrombosis combined with surgical intervention make the prognosis graver. Yet because of the ease of diagnosis of the condition, if such is promptly made and followed by immediate surgery, an occasional life may be saved.

Treatment of Peptic Ulcer by Means of Injections*

By

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and

C. R. MULLINS, M.D.

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THE relief of pain in peptic ulcer by means of daily injections of histidine monohydrochloride has been reported by numerous workers in the past two years. The claim is made that the pain usually disappears after several injections while the patients remain ambulatory and eat a normal diet. In evaluating the benefits of this method of therapy, control observations using some inert substance such as salt solution or distilled water usually have not been made. Such control studies are of particular importance because of the psychic factors in ulcer and also because of the tendency to spontaneous remissions in the disease.

The use of histidine in peptic ulcer originates from the observations of Weiss and Aron in 1933. They reported that it protected dogs against the formation of jejunal ulcer after the Exalto-Mann-Williamson operation. We have recently repeated this experimental work and also obtained some evidence of protection against ulcer with histidine. Weiss and Aron also studied the effect of histidine injections upon patients with active peptic ulcers and found that symptoms usually disappeared within a few days after the onset of injection therapy. This has been confirmed by Blum, Bulmer, Volini, Eads and others.

AUTHORS' WORK

The object of the present study was to compare a series of patients treated with histidine injections with a control group injected with normal saline. Eighteen ambulatory patients with active duodenal ulcer were used. The diagnosis was confirmed in all cases by X-ray examination. Ten of the patients had been treated in this clinic for previous attacks of ulcer and were considered to be "stubborn cases." All patients except one had been having daily epigastric pain immediately before the onset of injection treatment. None of the group had had a recent gross hemorrhage and none had pyloric obstruction as measured by the presence of a gastric residue six hours after a barium motor meal.

Twelve patients in the group were given daily intragluteal injections of 5 c.c. of normal saline solution. The other six patients received 5 c.c. of a 4 per cent solution of histidine monohydrochloride ("Larostidin," Roche) in a similar manner. The number of patients treated with histidine was limited to six inasmuch as many workers have definitely shown that the administration of this substance is usually followed by relief of pain. All of the injections were given by the writers and at the outset the patients were assured that relief of symptoms was to be expected.

The type of diet both before and during treatment is shown in the accompanying Chart. It will be seen that most of the patients were on a regular diet during the period of injection.

Because the patients were seen every day for treatment, it was feasible to keep a record of their daily symptoms. These were tabulated according to the custom of the Surgical Follow-up Clinic of the Presbyterian Hospital, a numerical value being given as a

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Submitted April 23, 1936.

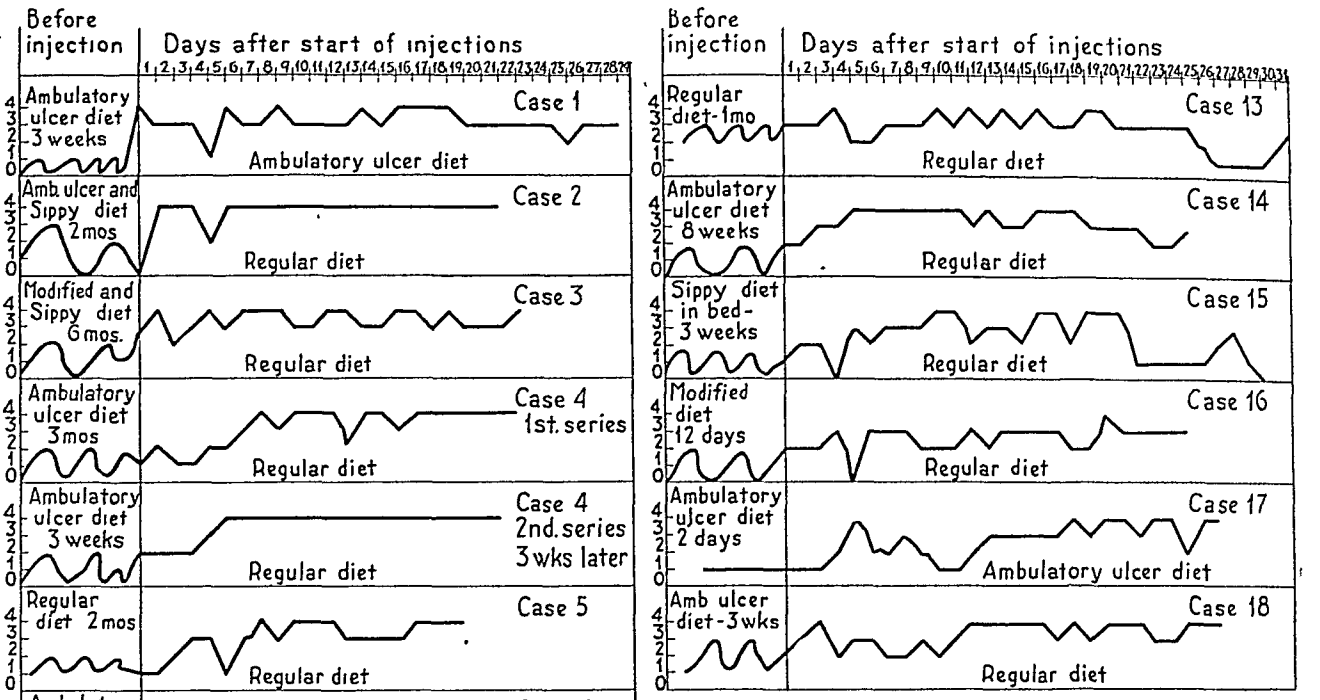


Chart I. Effect of injection treatment upon the symptoms in duodenal ulcer. Cases 1-12 received daily injections of saline. Cases 13-18 received daily injections of histidine monohydrochloride. The method of graphing the severity of symptoms is described in the text. Each graph represents the duration of the attack before injection treatment and the diet before and during treatment.

measure of the severity of symptoms during the previous 24 hours, as follows:

4 — symptom-free
3 — symptom-free except for slight "gas" or heartburn
2 — moderate epigastric distress
1 — severe pain, e.g., pain waking the patient at night; vomiting
0 — incapacitating symptoms

RESULTS

Eight of the 12 patients who received daily saline injections experienced complete relief of pain during treatment. This was in all cases very prompt and after three or four injections, the pain usually vanished. In one patient the pain disappeared as soon as injection treatment was suggested. Several individuals stated that they were able to eat foods which they had been unable to tolerate for a long time and testified that they had not felt so well in many years. The other four members of this group continued to have pain during the treatment.

Of the six patients who received histidine, four became symptom-free except for occasional "gas" during treatment. The other two subjects became definitely worse. One was a patient who was given the drug prophylactically. At the onset of treatment he was almost symptom-free but toward the end of the series of injections he developed symptoms of a recurrence of the ulcer.

All cases have been observed for one to four months since the course of injections was completed. Of the 12 cases who received saline, five remained well and seven had recurrent pain. The latter seven patients were subsequently placed upon frequent feedings, with alkalies and six of them experienced improvement. One (Case No. 4) continued to have severe pain. Upon this patient's request, a second series of saline injections was given and the pain again disappeared. After completion of the second course, the pain returned once more, and the patient requested a third series of injections.

Three of the six patients who received histidine remained well; one had a recurrence of pain relieved by diet, and two continued to have symptoms in spite of subsequent dietary therapy. One of the latter two

patients was hospitalized and subsequently died of hemorrhage from the ulcer.

COMMENT

The fact that daily injections of saline relieve pain in a substantial proportion of patients with peptic ulcer suggests that the therapeutic value of the various types of injection therapy for ulcer lies at least partly in the ceremony of giving the injection. Sandweiss has currently found that daily injections of distilled water relieved the symptoms in peptic ulcer in about one-half of his cases. These findings also emphasize the susceptibility of the patient with ulcer to the suggestions of the physician. It is our general impression that any new treatment for ulcer is successful in the majority of patients until the novelty has worn off. Furthermore, many people who are not improving with one form of treatment respond promptly to a change in therapy whatever that change may be. For these reasons it is not surprising that the daily injection of inert substances relieve the symptoms in peptic ulcer.

SUMMARY

1. Daily injection of saline for a period of about three weeks was attended by relief of pain in eight of 12 patients suffering from active duodenal ulcer.

2. Daily injection of histidine monohydrochloride (Larostidin, Roche) was followed by relief of pain in four of six patients with duodenal ulcer.

3. It is suggested that the successful results in this type of therapy in peptic ulcer are due to the psychotherapeutic value of the injections rather than the nature of the solution used.

4. Relief of pain in peptic ulcer by injection of salt solution emphasizes the importance of the psychic factor in the disease.

5. The evaluation of any therapy for pain in peptic ulcer should be controlled by comparison with the effect of inert substances administered in the same way.

Note: The histidine monohydrochloride (Larostidin, Roche) used in this study was supplied by Hoffman-La Roche, Inc.

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An Epidemic of Bacillary Dysentery in the Elgin State Hospital*

A Preliminary Report

By

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DIARRHEA occurring in a patient or a group of patients confined in an institution should be immediately investigated, the cause determined, treatment instituted, and necessary measures taken to prevent the spread of the disease if it happens to be infectious. The tendency to regard this complaint rather nonchalantly is fraught with considerable danger and may lead to serious consequences.

Bacillary dysentery is no more a disease limited to the tropics or the southern states. It is decidedly on the increase in temperate climes. Sporadic as well as endemic and epidemic types are being encountered with greater frequency and unfortunately are unrecognized until, in many instances, the autopsy table is reached.

INCIDENCE

Bacillary dysentery epidemics occur in institutions, camps, prisons and asylums. It was known as "asylum dysentery" because of the frequency with which it broke out in these places until it was proved to be bacillary dysentery by Duval and Bassett. Joseph Felsen, Emilie V. Rundlett, James Sullivan and Harold Gorenberg reported an outbreak of a typical Flexner dysentery in Jersey City in July, 1934, with a mortality of 2% in severe cases. L. L. Stanley, F. E. Garfinkle and W. P. Goddard reported an epidemic of Flexner dysentery occurring August 3, 1929, in the San Quentin Prison in which 946 inmates were afflicted and no mortality attributed to this disease. The duration of this epidemic was approximately two weeks. Felsen and A. G. Osofsky have just completed an epidemiologic study of an outbreak of Sonnè dysentery (closely related to the Flexner type) which occurred at the Bronx Hospital, N. Y., the latter part of December, 1933, and January, 1934. This outbreak occurred in midwinter and was traced to a child who had an interval appendectomy performed. Soon after discharge, a number of cases, only in children, although this organism may attack adults too, occurred in quick succession lasting twelve to twenty-four hours but unaccompanied by physical disability.

Epidemics occurring in the mountainous regions of Virginia have been reported by Higgins and also by

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Higgins and Silverman who show that this disease is on the increase in this state and other southern states. They assert that it will spread gradually throughout the United States unless steps are taken to check it.

The significance of this warning can be appreciated when one is cognizant of the increasing number of dysentery cases seen everywhere. This paper will be limited to a preliminary report of a severe epidemic of bacillary dysentery occurring at the Elgin state hospital. (This attack was confined almost entirely to the adult population and two young children who were exposed remained unscathed).

THE ELGIN EPIDEMIC

On June 18, 1935, a patient, Miss R. L., age 27 years, located in the Hirsch cottage (an "untidy" cottage of the institution) was seized with severe abdominal cramps, nausea, frequent and bloody diarrhea, prostration and high temperature (104° F. per rectum). She was transferred to the hospital for treatment and discharged July 9, 1935, with a diagnosis of non-specific enteritis. August 6, 1935, there was a recurrence of symptoms and she returned to the hospital for three days and was discharged. She remained in the cottage for seven days and August 16, 1935, returned once more to the hospital for treatment, this time being discharged in three days as cured.

There were no other cases observed until the 24th of June (7 days after the first case was reported) when two cases appeared: one in the same cottage (Hirsch) and another one in a male infirmary. These two cases remained in their respective wards for treatment. June 28, 1935, one more case appeared in the female infirmary. Then on July 2, 1935, thirty-five cases suddenly developed in Hirsch cottage—exactly fourteen days after the onset of symptoms in the first patient in this ward — and the epidemic began to spread throughout the institution in *bizarre* fashion until 475 patients and an undetermined number of employees, nurses, physicians and members of their families were affilicted. Of this number 357 were females and 118 were males. (See chart). The U. S. Veteran section of the institution remained singularly free of any involvement in this outbreak.

AGE INCIDENCE: The ages and number of patients are given in Table I.

TABLE I

Morbidity and Mortality

Age	No. of Cases	Deaths	Percentage
14-29	83	2	2.4
30-39	83	6	7.2
40-49	102	13	12.7
50-59	83	14	16.9
60-69	77	20	26.0
70-79	38	11	29 0
80-86	9	3	33.3

ETIOLOGY

Our experience in the determination of the etiological factor has been unlike many of those reported in the past. At the beginning of the severe outbreak in July, a few specimens of stools were submitted to the State Department of Public Health for examination and found to be negative for bacillary or amebic dysentery. Repeated cultures of stools made in the laboratories of the hospital showed B. coli only in pure culture and the epidemic was regarded as a non-specific type of entero-colitis. On August 8, 1935, the stools of two patients were reported positive for Hiss dysenteriae by the State Department of Public Health. August 9, 1935, ten blood specimens were submitted for agglutination tests and all but two were negative to Shiga and Flexner. Two agglutinated Flexner in very low dilutions; 1:80 and 1:40 and were regarded as negative. August 23, 1935, (9 weeks after onset), we began to proctoscope every new case and some old cases and took specimens directly from the base of the ulcers, if present, or the mucus from the mucosa and sent the swabs to the Department of Public Health for cultural studies. Up to December 15, 1935, we received only eight positive reports for Shigella parady-senteriae, variety Flexner. These same eight individuals had positive agglutination tests for Flexner. Three agglutinated in dilutions of 1:80; four in dilutions of 1:160, and one in dilutions of 1:320. All other specimens of blood submitted were entirely negative. In the course of this investigation we discovered one



Fig. 1. Shows sacculation and perforation of weakened wall of caecum caused by extensive ulceration and necrosis. Large ragged ulcers of variable sizes and with undermined edges and necrotic bases may be seen throughout this specimen. The intervening mucosa is intensively hyperemic and oedematous and assumes a polypoid appearance. This marked degree of involvement was pronounced in the caecum and ascending colon and gradually decreased in intensity in the distal portion of the large bowel, so, that only a moderate hyperemia and few superficial ulcers were noted in the rectum and sigmoid. The small bowel was only slightly hyperemic and not ulcerated. This patient was positive culturally and serologically.

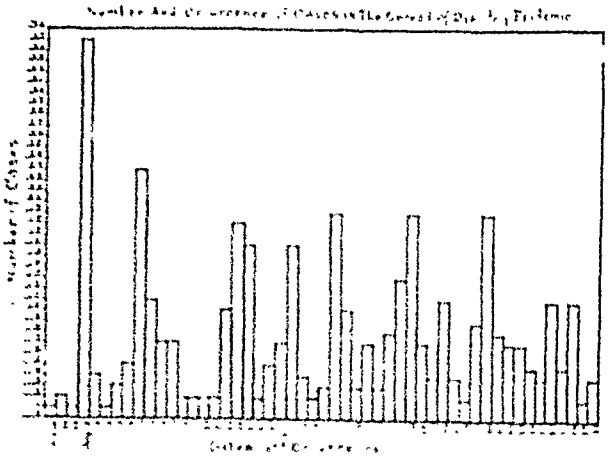


Chart Ia

food handler who was a typhoid carrier. These were the only positive bacteriologic and serologic findings determined from an aggregate of 488 proctoscopic and fifty-five blood specimens examined. Direct smears, the hanging drop, and cultural studies were made to exclude amebiasis, ulcerative colitis and typhoid.

The onset and course of the disease, proctoscopic appearance of the lesions and the bacteriologic and serologic findings seem to justify our conclusion that the epidemic was caused by the Shigella paradysenteriae, Flexner variety.

EPIDEMIOLOGY

Bacillary dysentery is usually conveyed to individuals through the ingestion of water, milk or food contaminated by carriers. Excreta of active cases are extremely contagious and the most scrupulous care in washing hands, and in some cases, the body, is necessary to prevent the spread of this disease to epidemic proportions.

The origin of this Elgin epidemic is still a matter of uncertainty. Investigators from the State Department of Public Health made a survey, recommended cultures of water and milk, and offered certain suggestions relative to changes in the water and milk supply and food containers.

In addition we made a complete and thorough survey of the 214 patients and 46 employee food handlers who were working at the beginning of the outbreak. All of these individuals were proctoscoped and all suspicious cases were immediately dismissed from food handling duties.

The disease is definitely not water-borne because the Veteran group which had the same water supply but not the same milk or food supply was not affected.

It might have been milk-borne. The morning milk supply for the entire institution, except the Veteran section, is furnished by cows on the hospital farm and is not pasteurized. Specimens of milk examined at the time showed an excessively high bacterial count but no dysentery. The afternoon and evening supply is furnished by city dairies. In a survey of all food handlers we found one patient with an active case of dysentery who worked around the cow barn. He made no complaint at any time and did not appear ill. He refused at first to submit to an examination and only after much persuasion finally consented, when we were amazed to find that the entire bowel up to 18 cms. was hyperemic, and ulcerated and some of the mucosa, distally appeared granular and pitted as a result of recently healed ulcers. Scrapings from the base of the ulcers were positive for Shigella paradysenteriae, Flexner variety, and his blood agglutinated Flexner in dilutions of 1:160. Another patient who has been a milker was found to have a hyperemia of the bowel. He denied having had diarrhea. These two patients were immediately isolated. The latter returned to work in the dairy after two subsequent cultures proved to be negative.

Upon investigation we found some individuals who did not drink milk but had been afflicted with dysentery. However, this does not entirely exclude this source as a possibility because, we are sure, cream was consumed by these individuals.

Rosenau states that there is no record of a milk-borne outbreak attributable to properly pasteurized milk.

Contaminated food as a likely source is very probable. Our attention was directed to the fact that on the farm colony no case of dysentery was noticed until two days after their kitchen was closed and food was received from the general kitchen serving the rest of the institution. In the examination of food handlers fifteen patients and three female employee food handlers were temporarily dismissed because of suspicion of being carriers. One of the employees (female) who worked in the physicians' dining room was found to have a positive culture for Shigella paradysenteriae, Flexner variety, and her blood serum agglutinated Flexner 1:160. She was isolated until three successive cultures were negative and has now been assigned to some work in the laundry. All the others returned to work as soon as their cultures were found to be negative on three successive examinations.

All the buildings were properly screened, but it was impossible to keep flies from entering the various kitchens and dining rooms because doors were kept open for long periods of time to permit patients and employees to enter and leave. Many flies were also

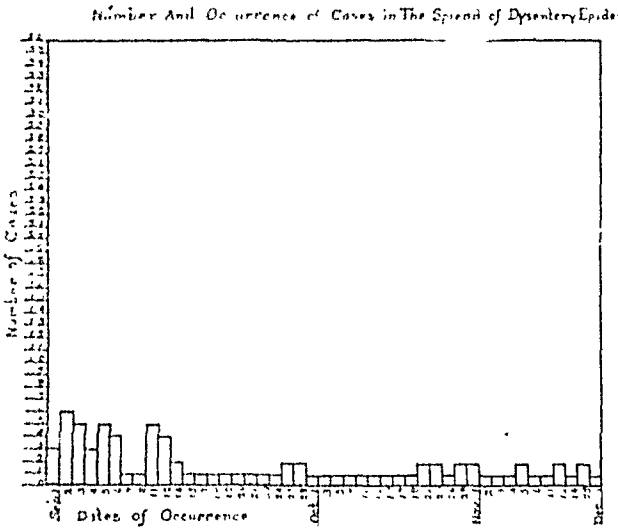


Chart Ib

carried in by patients. It is quite possible that flies may have contributed to the spread of the disease.

BACTERIOLOGY

Excepting the fecal cultural work which was performed before one of us (L.H.B.) arrived at the institution, all of the specimens submitted for cultural studies to our laboratory and to the laboratories of the State Department of Public Health were taken through the proctoscope directly from the base of ulcers or from the mucus deposit on the wall of the bowel, and some plated immediately on Endo medium. A total of 260 plates were thus inoculated and carefully cultured and worked up by the State Department of Public Health. In addition 228 swabs were handled in a like manner. Of this number only eight were found to be positive for dysentery—amounting to less than ½ of 1%, an infinitely small showing for an epidemic of this size.

Unfortunately this intensive work was not started until two months after the beginning of the outbreak and for this reason probably did not yield good results. Nevertheless, there were 117 acute cases observed during this period and still the number of positive bacteriologic results was not increased, probably due to delay in incubating the inoculated media. Our bacteriological experience has amply proved that these organisms are difficult to isolate even when using the direct method of obtaining specimens, but that repeated cultural studies should be made in all suspicious diarrhea cases, preferably securing specimens through a proctoscope.

SYMPTOMATOLOGY

Period of Incubation: The exact period is difficult to determine. Seven days elapsed before other cases appeared after the first one was reported. Following this the period of incubation was much shorter. The prevailing opinion is that the incubation period is between one and seven days.

Mode of Onset: The onset varied so much in intensity that we can conveniently divide it into three types.

Symptomless Type: A few cases were accidentally discovered in the course of our survey who denied having had diarrhea or any other symptoms of dysentery. In one case, a dish washer in one of the kitchens had a profuse diarrhea at the time of examination and subsequent proctoscopic examination revealed a hyperemic bowel. His temperature was normal, he did not complain of any abdominal cramps and felt perfectly well. His cultures and serological examinations were negative. In another instance described above the patient made no complaints whatsoever referable to the gastro-intestinal tract, was afebrile and did not appear ill. He was positive proctoscopically, culturally and serologically for Shigella paradysenteriae, Flexner variety.

It would be futile to venture a guess as to the probable number of symptomless cases in the institution unless every patient were thoroughly examined—an almost impossible feat. However, we are sure there were many cases of this type which were overlooked because the symptoms were so mild in character and the mental condition such that the patient was not cognizant of it, or too indifferent to complain.

Mild Type: The preponderance of cases noted, amounting to 289, were mild in character with temperatures ranging from normal to 101°. (Duration was from one to four days). They did not appear very ill and had little tendency to tenesmus and bloody diarrhea. These cases, usually young individuals, were treated in the ward in which they happened to occur.

Severe Type: There were 186 recorded cases of this type occurring in the most debilitated individuals, in the higher range of ages. The symptoms appeared suddenly, ushered in with marked prostration, pyrexia of 101° which rapidly rose to 106°, and in two cases to 107.6°, nausea and vomiting, and severe tenesmus and excruciating pain over the entire abdomen, particularly in the right lower quadrant. Diarrhea was extremely frequent, and the stools contained variable amounts of blood from a good sized hemorrhage to streaking, mucus, mucopurulent material and no fecal matter. The patient suffered a great deal from an incessant and annoying desire to evacuate the bowels. The number of stools was large, often reaching to 30 or 40 a day, and the quantity evacuated was very small.

As the disease progressed the character of the stool changed and often pseudomembranous casts were passed. The stool was extremely offensive, had a characteristic odor much like that of semen and was no longer watery but serous and dark from altered hemoglobin. Vesicle tenesmus characterized by marked discomfort and frequency of urination was a troublesome symptom. The mouth was dry and the tongue swollen and heavily coated. As a result of the excessive loss of fluid from the body the patient complained bitterly of thirst.

The disease, usually self-limited, ran a course of from 10 days to two weeks. Some cases became subacute and ran a course of a month or more, and a few became chronic. A number of patients became extremely toxic and death ensued within the first few days and in some cases in a few weeks.

Chronic Type: We still have under our care six chronic cases who have periods of remission. They are markedly emaciated, afebrile, and have frequent stools: dark, serous, bloody and offensive. There have been times when their stools were formed and they had one or two evacuations daily but this period of improvement was of short duration.

DIAGNOSIS

The diagnosis of this disease would have been readily made if the cultural and serological tests were all positive. Often it is impossible to isolate the causative organism and one must rely, if dealing with an epidemic type of dysentery, on many other factors. The clinical history was strikingly similar in every case. In addition other findings contributed to the support of the diagnosis of bacillary dysentery.

Physical examination in the mild type revealed very little that was significant except some tenderness over the caecum and sigmoid regions on deep pressure. However, in the severe cases the patient appeared acutely ill, very pale, ran a high temperature, had a rigid and sometimes distended abdomen which was very tender to palpation, particularly over the large colon. There was no involvement of the liver or spleen.

Proctoscopic study of all cases is unquestionably indispensable in the determination of the nature of the diseased condition with which we are dealing. A total of 595 proctoscopic examinations were made (by L.H.B.) in the course of our work. The patient, if cooperative and not too ill, was placed in the knee

shoulder position. If this was impossible, he was placed over the side of the bed or table with the head resting on a pillow placed on a low chair or floor. A well lubricated index finger was introduced slowly and gently to determine the condition of the sphincter, anus, and lower rectal ampulla. (Invariably in dysentery, especially if severe, the sphincter was markedly spastic). This was followed by the introduction of the proctoscope. Not unmindful of the fact that in bacillary dysentery the passage of the proctoscope is painful (a diagnostic point of interest) much care was taken to make the procedure tolerable. In most instances we were successful in reaching the recto-sigmoid junction without causing unnecessary discomfort.

The appearance of the proctoscoped field in acute cases was characteristic. The mucous membrane was intensely inflamed, in many cases oedematous and actually caused a narrowing of the lumen of the bowel. Slightest trauma produced a bleeding surface which was sometimes profuse. There were numerous superficial ulcers covered with a pseudodiptheritic membrane usually seen on the crests of the folds of the mucous membrane running transversely to the lumen of the bowel. These ulcers were irregular, jagged, and not undermined. As these small discrete ulcers began to spread and coalesce until they formed large irregular confluent patches the folds of the mucous membrane seemed to disappear. The intact mucous membrane, intensely inflamed, presented peculiarly geographical areas which often became polypoid in character. In some cases the process of necrosis was so extensive that large sheets of this necrotic tissue could be seen in the lumen of the bowel.

Most of the patients were observed from time to time so that many received from two to three or more proctoscopic examinations. As the ulcers gradually disappeared and the oedema and hyperemia subsided, the mucosa assumed a granular appearance and many small dimpled areas could be seen, caused by the healed ulcers. Healing begins at the distal end of the rectum (usually the muco-cutaneous junction) and gradually continues upward to the other portions of the colon. We observed no strictures directly attributable to this disease in this series of cases.

COMPLICATIONS

Only one case of arthritis was noted which occurred in an employee a few weeks after onset of mild symptoms. However, she gave a history of a previous attack of arthritis about seventeen years ago. Four patients developed peritonitis due either to the extension of the inflammation to the serous layers of the bowel or to perforation. In one case, a chronic type, a perforation of the caecum was found on autopsy.

TREATMENT

This consisted of rest in bed, limited liquid followed by high caloric, non residue diet, belladonnae, bismuth subcarbonate, and occasionally an opiate. Irrigations with pot. permanganate were given to hospital cases. In severe toxemia intravenous saline and glucose was given as indicated.

We resorted to the use of serum in a limited number of cases. Serum acts in two ways: neutralizes the toxins liberated by the infecting bacilli, and destroys the bacilli themselves. A large quantity of the serum is necessary to combat the effect of the absorption of toxins due to its low antitoxic content, and should be given intravenously early in the disease. Polyvalent, Shiga and Flexner, dysentery serum (Lederle) in 50 c.c. doses, mixed with 50 c.c. of normal saline, was administered intravenously to nine patients. In all cases there was an elevation of temperature from 100° to 105°. Two cases expired in a few days; one case received 100 c.c. and later on another 100 c.c. of convalescent serum and finally expired. An employee, 50 years of age, severely ill, who received the serum within twenty-four hours after onset of symptoms, experienced relief of abdominal pain, cessation of tenesmus and frequent bowel movements; and within five days all symptoms disappeared and the extensive lesions of the bowel wall almost entirely healed. He recovered completely in seven days. Of the remaining six patients, three recovered entirely and three became chronic.

At this time Dr. Read suggested the use of convalescent serum and through the courtesy of the Michael Reese Serum Center a supply was prepared for our use. 250 c.c. of blood was drawn from each of twenty-eight convalescent patients and twelve vials containing 100 c.c. each of mixed serum was prepared. We administered 600 c.c. to five different patients. There were no reactions following its use, no elevation of temperature, and apparently no change in the condition of the patients.

Sodium thiocyanate as suggested by Mitchell and Goldman was administered to some of the patients, acute and chronic types, but without appreciable effect. This result corroborated the findings of the authors that this preparation was useless except in B. Shiga dysentery.

FATALITY

There were sixty-nine deaths—forty-five females and twenty-four males—making a gross fatality rate of about 16.5%. This would doubtless be much lower were we to include the indeterminate number of unrecognized patients in our calculations.

Sex apparently does not influence the rate. Female death rate was about 8% compared to the male of 6%,

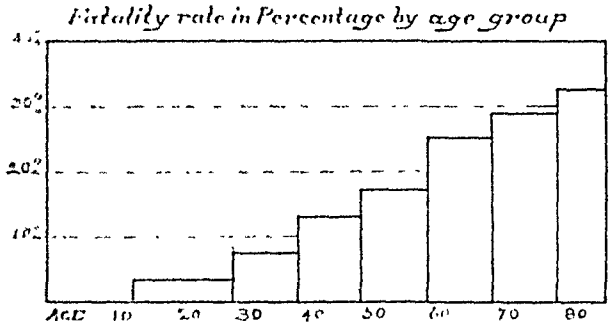


Chart II

the difference probably due to the fact that there were twice as many females afflicted.

Age influenced the fatality rate considerably as shown in Chart II. The sharp increase in fatality with the age of the patient is strikingly pictured.

PATHOLOGY

The disease process is usually limited to the large colon and in very severe cases may mildly affect the mucosa of the small bowel as far as the pylorus. The

caecum, the various flexures, hepatic, splenic, and sigmoidal and the rectal ampulla are greatly affected. The disease usually begins at the most proximal end, the caecum, and gradually spreads to the rectal ampulla. The mucosa and submucosa are intensely inflamed, oedematous, and dark red in color and covered with ulcers. These superficial, shallow ulcers, discreet or confluent, are irregular, jagged, and not undermined, and are covered with a pseudo-diphtheritic membrane which is easily removable. The folds of the mucosa may become thickened and assume a polypoid or cystic appearance. In far advanced cases the muscularis and serosa are involved and, due to the extension of the necrotic process, the wall of the bowel becomes weakened and perforation may ensue or gangrene may develop.

SUMMARY AND CONCLUSIONS

1. Every case of diarrhea occurring in an institution merits a relentless investigation due to increasing incidence of dysentery in temperate climes.

2. An epidemic of dysentery continuing over a period of more than five months, atypical in character, occurred throughout the Elgin State Hospital with the exception of the veteran section.

3. In a population of 4,500 there were 475 patients and an undetermined number of physicians, nurses, employees, and members of their families afflicted.

4. The causative agent was the Shigella paradysenteriae, Flexner variety.

5. The primary source has not been definitely determined. Carriers have been discovered who could have easily polluted both the milk and food supply. However, part of the milk supply is not pasteurized which makes this a potent source for the spread of any infection and particularly bacillary dysentery.

6. A total of 488 endo plates were inoculated and cultured with specimens taken directly from the base of ulcers through a proctoscope and only ½ of 1% were positive.

7. The usual course of the disease varied from four days to two weeks, except in few chronic cases.

8. An intensive proctoscopic study was made of all cases, including food handlers, totalling 595 examinations. This afforded an unusual opportunity to view the various changes that took place in the rectum and bowel during the course of the disease.

9. Limited experience with the use of polyvalent serum has demonstrated its value if administered early and in sufficiently large doses. Convalescent serum prepared for our use has had no effect.

10. Mortality was 14.5% and affected debilitated patients in the higher range of ages.

ACKNOWLEDGEMENTS

We wish to express our appreciation and our indebtedness to H. E. McDaniels and V. M. Ryan, bacteriologists of the Illinois Department of Public Health Chicago Laboratories, for their excellent work in the bacteriological and serological study of these cases; to Drs. S. O. Levinson and A. A. Platt of the Michael Reese Serum Center for the preparation of the convalescent serum; to Dr. Chas. F. Read for his invaluable aid and suggestions, and to members of his staff for securing necessary data.

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The Peptic Ulcer Syndrome in the Negro*

Clinical and Statistical Evidence on Psychogenic as Against Racial Factors in the Etiology of this Syndrome

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FROM the enormous literature‡ dealing with the etiology and pathogenesis of peptic ulcer it is apparent that more than one cause is active in the genesis of peptic ulcer. The majority of clinicians today hold that certain of these causes can be grouped under the so-called "systemic factors" (30). These are taken to include a great number of psycho-physiologic processes and peculiarities that affect man alone, such as physical characteristics (9, 30, 31, 33), constitutional factors (13, 34, 38), certain diatheses (13), familial tendency (1, 20, 29), sex (30, 31), general health and resistance (30), mental and nervous reactions (1, 3, 4, 10, 19), emotions (1, 5, 10, 33), moods (18, 25), and tendency to perseverance (1, 30). Occasionally they include even personal achievements (30) based on intensive study or work, and the complexities of modern American life, characterized by stress, strain and speed. In other words, certain selective features of anthropometry, personality, sex, and environment which seem to be playing an important role

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‡In 1931 Cushing stated that the references on peptic ulcer etiology and pathogenesis, the number of which was listed by Moeller as 325 in 1911, had probably quadrupled by that time. In 1936, therefore, the number is surely much higher. Hence the references listed for this paper were, with few exceptions, strictly those dealing with the neurogenic or psychogenic phase.

TABLE I

Location of Hospitals	Number of peptic ulcer patients admitted in one year	Of These		Percentage of Negro ulcer patients	Percentage of peptic ulcer cases of total hospital admittance	Percentage of Negro patients in total admittances
		Whites	Negroes			
Ill. Chicago (C. C. H.)[1]	604	527	77	12.7	0.88	27.7
Ill. Chicago (R. & E. H)[2]	65	63	2	3.0		
Fla. Jacksonville	2	0	2*	100.0	0.24	
Fla. Miami	37	34	3	8.1		
N. Y. New York	108	100	8	7.4		8.0+
N. C. Durham	99	81	18	18.1	.	
Ga. Atlanta	215+	117	98	45.5	0.66	44.0
Tex. San Antonio	15	15	0	0		..
Tex. Galveston	35	27	8	22.9		
Ala. Birmingham	74	28	46	62.1		
La. New Orleans	52	47	5	9.6	..	
Total	1306	1039	267	25.69		

*All patients are Negroes.
+Two years' admittance.
1. Cook County Hospital.
2. Research and Educational Hospital.

in the genesis of peptic ulcer are discussed under the heading of systemic factors.

Although some authors speak of a "peptic ulcer race" (9) in a certain etymological sense, the racial factor in an ethnological sense, has been rarely considered and then only superficially. In fact, racial selectivity has been mentioned only by one writer (31) while another (30) has called attention to the rather rare occurrence of peptic ulcer in the colored as compared with the white race. Thus Rivers (25) reports the surprising fact that of two hundred Negroes interviewed in a certain county in Texas only three per cent gave a history of indigestion, and only one individual gave symptoms suggestive of peptic ulcer. This appeared the more significant to him because those Negroes had lived on a non-balanced diet, dissipated recklessly, used tobacco and alcohol excessively, lived under poor hygienic conditions, were without work, and scarcely knew the source of their next day's food. Racial selectivity, as a factor *per se* has been stressed by Robinson (31) who states "the Negro and lesser pigmented races are immune to the disease (peptic ulcer); the white race alone is susceptible. The pure blooded Negro is practically immune to the disease because of hereditary differences of psychological structure and function. The Negro race in its evolutionary ascent has not as yet acquired the habit of worry so peculiar to the white race under pressure of routine civilized living."

AUTHOR'S STUDY

The present study is an outgrowth of the discrepancy between the above quoted statement and the observations made by this writer in the course of his work at the Cook County Hospital in Chicago. If the Negro is "practically racially immune to peptic ulcer," then peptic ulcer in the colored race should be extremely rare. If, on the other hand, peptic ulcer is rare in the Negro in the agricultural areas of the South and common in the Negro in the industrial areas of the North, then the Southern Negroes are protected from peptic ulcer by special factors other than race.

The first fact that became apparent to the writer was that the Negro patients with peptic ulcer whom he interviewed were vastly different individuals from the indifferent types of Texas Negroes described by Rivers (30). Although on the whole somewhat less apprehensive and less complaining than white ulcer patients, they nevertheless were far from being indifferent. They worried about their health, lack of economic security,* their diet, and other things too numerous to mention. In short, these Negroes lived under the same conditions of stress and strain as the whites, and reacted to them in substantially the same way.

In order to check the discrepancy between these observations and the conclusions reached by Robinson (31), the writer proceeded to gather statistical evidence. In the course of 1934, 67,831 patients were admitted to the Cook County Hospital (including readmittances). Of this number, 604, or 0.88 per cent were diagnosed peptic ulcer clinically and roentgenologically. Seventy-seven, or 12.7 per cent of these were Negroes. Ninety-seven, or 16 per cent, of the 604 ulcer cases were patients admitted with perforated peptic ulcer, and of these, eleven, or 11.3 per cent were colored. In the gastro-intestinal clinic, of 605 active cases (*i.e.* reporting to the clinic at least once in six months), ninety-seven, or 16 per cent, are Negroes: eight, or 8.2 per cent of them having had operations for perforated peptic ulcer.

It was further noticed that in these colored patients the average duration of symptoms referable to the gastro-intestinal tract was about five years, while the average time they had been in Chicago was about eleven years. The relation of the average time lived in Chicago to the average duration of ulcer symptoms

*See Footnote at end of this contribution.

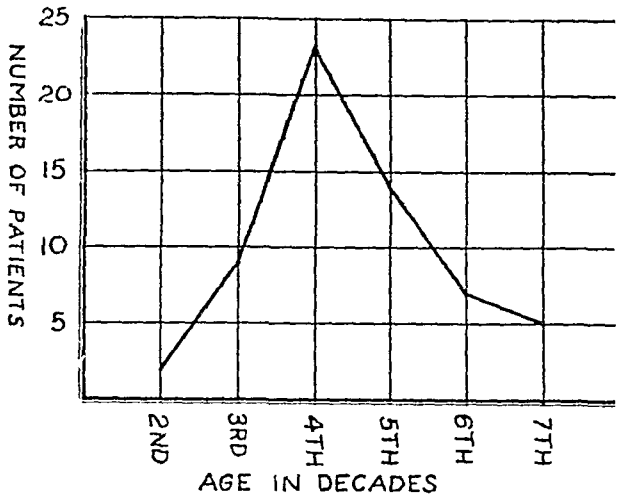


FIG. 1 THE DISTRIBUTION OF PEPTIC ULCER IN DIFFERENT AGE GROUPS

is quite striking in this ratio. It should be noticed that these patients lived in this environment for some time before the symptoms of peptic ulcer appeared. Furthermore, individual figures are even more impressive, as they give definite evidence that the symptoms referable to the gastro-intestinal tract appeared often many years after their arrival in this region. Indeed, only in three patients was there a history of gastro-intestinal disturbance dating back to their residence in the South.

In order to check further the validity of these statistics, data were gathered relative to Negro ulcer patients and Negro admittances from other hospitals in Chicago and elsewhere. Thus it was found that of all patients admitted to the Cook County Hospital within a period of one month (considered conclusive for our purpose), 27.7 per cent were Negroes. Returns on questionaires received from other free hospitals are given in Table I.

It is obvious from these data that the Cook County Hospital is not unique in having a fair proportion of colored peptic ulcer patients.

Sixty colored patients reporting regularly to the gastro-intestinal clinic were chosen at random and interviewed in regard to their age, habits of smoking and drinking, diet, living conditions, number of dependents, schooling, and economic adjustment. These patients had also their blood pressure and degree of gastric acidity determined. The results obtained are given below in graphic form.

These graphs clearly show that (1) the condition is most common between the third and fourth decade, when responsibilities are usually greatest; (2) habits were essentially moderate, forty-five being habitual smokers and only two indulging in alcohol beverages; (3) diet was fair on the whole, although none of them complained of poor food; (4) living conditions were tolerable; (5) nearly two-thirds of them had two or more dependents; (6) only nine had no schooling, but the remainder had from four to eight years of grammer school, ten of these having attended high school and three even college; (7) only twelve were employed, twelve of them being unemployed because of poor health; (8) most of them had a systolic blood pressure range of 120 to 140, and a diastolic range of 70 to 90; and (9) the majority of patients had a free acidity above thirty degrees, several of them having free acid values in excess of seventy degrees, but three had an achlorhydria (*i.e.* with one Ewald meal).

The results of the analysis of these social-economic factors clearly manifest the bases for a number of psychic stimuli to which these patients were exposed. The worry, fear, anxiety, and other emotional tensions present in these individuals were probably of sufficient strength to affect the neuro-vegetative center and thus to produce, through their autonomic outflow, derangements in the function of the gastro-intestinal tract (15), which ultimately led to subjective and objective symptoms characteristic of peptic ulcer. This does not imply that mental impulses mediated by the neuro-vegetative center in the diencephalon are the sole cause of peptic ulcer formation, but it does mean that these impulses are of paramount importance, and that locally acting stimuli are only supplemental in nature. It also suggests that these psychogenic-neurogenic impulses act as the exciting factor (32) of a peptic ulcer syndrome, and that without them the local component is symptomless. This would explain why a recurrence of peptic ulcer symptoms is experienced more often after some upset in the psychic, rather than in the somatic component (38, 1, 3, 10, 28, 37). It would also tend to explain why Negroes in industrial centers are more likely to have peptic ulcer symptoms even though the local stimuli (diet, etc.), are, if anything, less severe in the urban (Northern) than rural (Southern) Negro. Finally, it shows why the results of peptic ulcer treatment are much better and recurrences rarer in clinics, where the patients are from smaller communities than in the clinics which treat predominantly city dwellers (33). The only reason for this difference is that in the latter clinics the patients are individuals who are under the influence of psychic stimuli to which the patients of the first clinics are either not exposed at all, or are exposed only to a small degree.

DISCUSSION

The pros and cons (11, 12, 16) of the systemic factors in the genesis of peptic ulcer have been discussed by a large number of clinicians, some of them

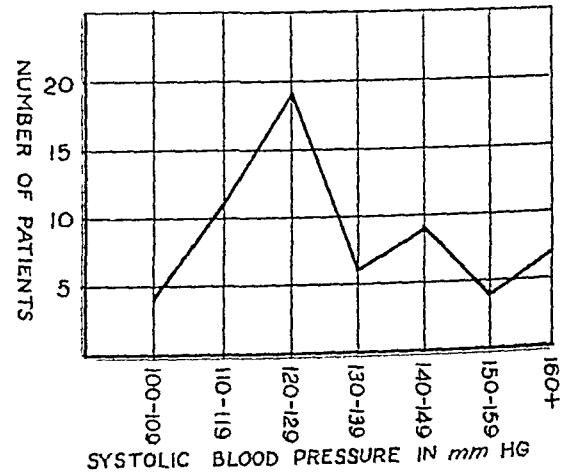


FIG. 2 SYSTOLIC BLOOD PRESSURE IN PEPTIC ULCER PATIENTS

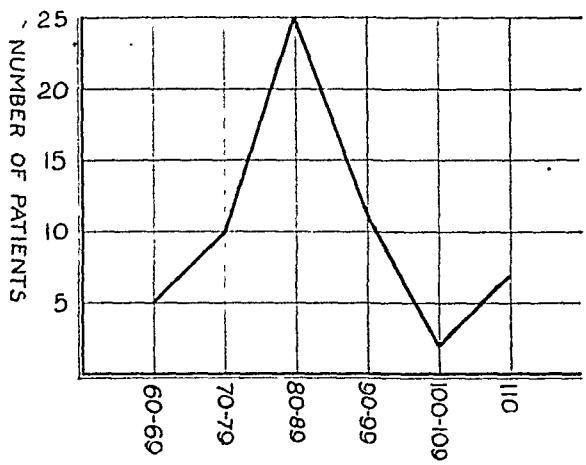


FIG. 3 DIASTOLIC BLOOD PRESSURES OF PEPTIC ULCER PATIENTS

outstanding figures in the medical world, yet none of them has referred to racial selectivity as playing an important, or in fact any, role whatsoever. Only recently, Moschcovitz (27) in listing several syndromes, among them gastric and duodenal ulcer, which he believes to be psychogenic, stated "that such diseases are but exaggerations of normal function; they are essentially human diseases and cannot be produced experimentally in animals; they rarely occur before the emotive and affective powers are fully developed; their life cycle is characterized by a great tendency to recurrence; their incidence bears a strong relation to world crises or great emotional waves" but failed to mention that they occur only in the white race. It would, therefore, seem strange indeed that all these men should have overlooked such an important factor, if it actually exists. Even if the continental writers are eliminated from this group of clinicians, as their material is based on white patients almost entirely, there still remains a considerable number of American authors whose material consisted of mixed races (Whites and Negroes). When such comprehensive reviews on the subject as have been written by Cushing (8), Alvarez (1), Smithies (35), Crile (6, 7), and others fail even to suggest a racial selectivity factor, its existence becomes quite doubtful. If, moreover, various observations and statistics show that peptic ulcer is found in a comparatively high percentage of Negroes in different geographical areas, then the theory of racial selectivity in the genesis of peptic ulcer becomes untenable.

In referring to racial selectivity as a unique feature of peptic ulcer, Robinson (31) states that the colored race is "skipped by the disease" because of hereditary differences in psychological structure and function; and that in its evolutionary ascent it has not acquired as yet the habit of worry so peculiar to the White race under pressure of routine civilized living. From this assertion it is inferred that the Negro belongs to a more primitive race, and has by heredity a different psychologic structure and function. The question thus arises, first, whether this assertion is correct and peptic ulcer is found less frequently in the Negroes because of their race and inherent psychological structure and function, or, secondly, whether this statement is incorrect and the lesser incidence of peptic ulcer in the Negroes is due to the environment which has protected most of them from the effect of harmful psychogenic influences. The first question must be answered in the negative. The second question is best answered in the affirmative.

The subject of racial differences has recently been covered by Klineberg (23) in his *Race Differences*. After an exhaustive survey of the voluminous literature on this subject the author summarizes the present day attitude of psychologists, based on objective findings. He concludes that the characteristics that distinguish human races are morphological, and that physiological, psychological and even pathological differences remain to be proved (*p. 18*). He disposes of the fallacious assumption that one race is more primitive than another *(p. 36)*, and goes on to say that we have no right to regard every Negro as differing from every White, or to expect that all Negroes will behave similarly in similar situations (*p. 20*). He establishes definitely the immense influence of environmental, social, and economic factors on the results of intelligence tests, on which the presumptuous notions of racial differences are based. The importance of these factors is most clearly apparent from the results of intelligence tests given to similar groups of Negroes in different geographic areas showing that the Negroes in the North, Northeast, and Northwest are much superior to those in the South (*p. 183*). The importance of the environment is supported by similar conclusions reached by Lorimer and Osborne (24), (*p. 198*) who state "Among large regional groups in the United States differences in economic and other environmental factors, such as climate, education, and so forth may be sufficient to explain cultural-intellectual differences without recourse to genetic explanation."

Since, however, not only intelligence but personality also has been used to differentiate the races, Klineberg (23) analyzes the findings of a number of authors who tried to prove or disprove these conceptions, and concludes that objective measurements of "non-intellectual" traits also failed to demonstrate racial differences (*p. 207*), and that hence *culture* appears to determine situations that arouse emotional responses, to regulate the extent to which these responses are overtly expressed, and the particular forms which their expression may take (*p. 287*). His final conclusion is that the case for psychological race differences

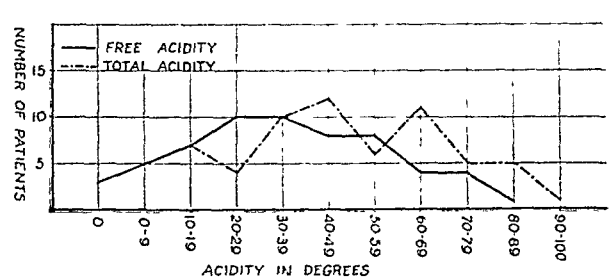


FIG 4 DISTRIBUTION OF PATIENTS ON THE VARIOUS LEVELS OF FREE AND TOTAL ACIDITY

has never been proved and that there is no scientific evidence of racial differences in mentality (*p. 345*).

From the statistical data offered and the various critical comments on the role of systemic factors in the genesis of peptic ulcer, nothing seems to point to a racial selectivity. Moreover, from the conclusions cited in regard to psychological differences between races, a racial selectivity based on differences of psychological structure and function appears to be scientifically intolerable. It is manifest that the role of environmental stimuli on the vegetative nervous system in the production of peptic ulcers in Negroes (as in Whites) has been substantiated by the conclusions of various writers. If the differences in emotional response are not to be explained on the basis of innate racial make-up, but on the basis of *culture* (the latter being used to mean attitudes and experiences which an individual receives from the society of which he is a member), then it stands to reason that the Negro in the North will respond to emotions (overt or repressed) and other stimuli to the vegetative nervous center in the same manner as do other members of the society to which he belongs, society here including both Whites and Negroes. Similarly, the Southern Negro will less frequently be beset by peptic ulcer, as the White members of his society are also affected but little by this syndrome as compared to their Northern brethren.

In closing, it may thus be stated that the clinical and experimental observations of a large number of investigators, and the study of our own clinical material, justify the following conclusions: First, that peptic ulcer is not due to any one specific cause—selectivity or unique feature—but to a combination of a variable number of factors which have been best described by Rivers (30). Secondly, that although hyperchlorhydria is not a prime requisite for peptic ulcer (36), most peptic ulcer patients, nevertheless, show hyperchlorhydria, hypersecretion, hypermotility, and hypertonicity (17, 37). The last is especially marked in the pyloric portion, and is the precursor of pyloric spasm which is believed to play an important role in the genesis of peptic ulcer (21). Thirdly, that all these gastric phenomena can be produced by the stimulation of the neuro-vegetative center in the diencephalon, a center which is easily affected by psychic influences (8, 14, 22, 26). Fourthly, that on the basis of these observations it may be assumed that digestive disturbances, hyperacidity, and even ulcer, will occur in vagotonic individuals who, according to Cushing (8) are under the domination of such psychic stimuli as overt or repressed emotions, incidental or continued worry, anxiety, heavy responsibilities, etc., alone, or in combination with locally acting factors, such as improper food, excessive food and drink, etc. Finally, that these vagotonic individuals do not belong exclusively to the white race, but may also be members of the colored race, a fact which explains why peptic ulcer is not as rare in the Negro as the theory of racial selectivity would lead one to believe. This is of importance clinically in that it suggests that the clinician must approach the problem of peptic ulcer in the Negro with the same attitude as he does in the White patient.

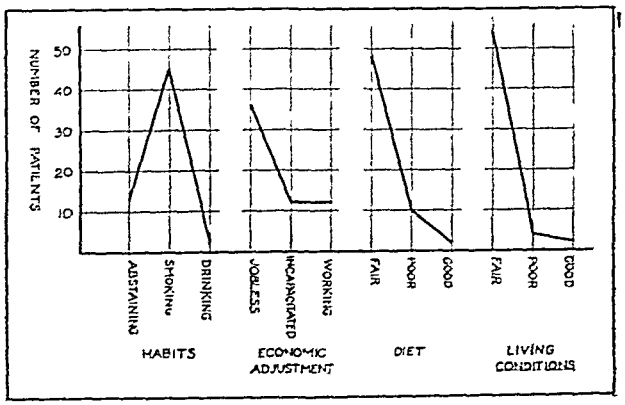


FIG. 5 PATIENTS' HABITS IN REGARD TO SMOKING AND DRINKING, ECONOMIC ADJUSTMENT, DIETARY REGIMEN, AND TYPES OF DOMESTIC SURROUNDINGS

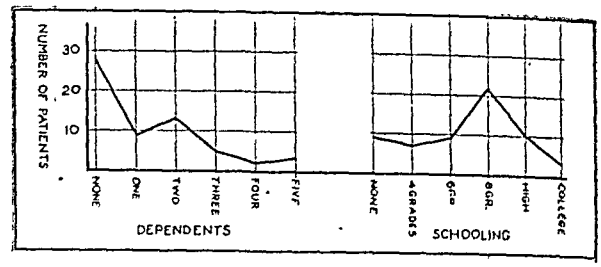


FIG 6 PATIENTS' RESPONSIBILITIES AND EDUCATION AS INDICATED BY NUMBER OF DEPENDENTS AND YEARS OF ATTENDANCE AT SCHOOL

SUMMARY

1. Negroes constituted 12.7 per cent of all the peptic ulcer patients admitted to the Cook County Hospital during the period of one year, while slightly higher or lower percentages are found in other hospitals admitting both White and Negro patients.

2. Environmentally conditioned psychic factors play an equally important role in the genesis of peptic ulcer in White and Negro patients.

3. Northern Negroes, hence, of industrial centers, just as the Whites of these areas, are more frequently subject to peptic ulcer than Southern Negroes and Whites of agricultural areas, respectively.

4. The theory of racial selectivity as a unique feature of the peptic ulcer syndrome could not be substantiated, while the hypothesis on which this theory of racial selectivity is based is contrary to the latest conceptions of comparative psychology.

I wish to express my sincerest gratitude to Dr. M. H. Krout and Dr. H. A. Singer for their helpful suggestions during the preparation of this paper.

Footnote: In the phrase "worry about lack of economic security" we included a number of things which seemed to worry these patients, particularly as gathered during the interviews with them. Some of the more outstanding things that worried the greater number of these individuals are given below: insecure jobs; disagreeable work; small pay; insufficient money for rent, gas and electricity with the associated fear of eviction and shutting off the gas or electricity; lack of carfare to go about; lack of money for personal spending; small relief allowances; friction with the case worker and landlord; separation of family members due to breaking up of home; improper clothing for public appearance; insufficient clothes for themselves and the children; irregularity of school attendance by their children, because of lack of certain parts of the clothing; lack of opportunities for their children; loss of property and fear of losing certain possessions, etc.

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The Differentiation of Surgical and Medical Groups of Jaundice*

By

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WHEN confronted by a patient with jaundice, the inevitable question arises: Is surgical relief of obstruction indicated? If the answer is to be affirmative, it is desirable to establish the fact as early as possible so that preoperative measures can be properly carried out and the risks attending prolonged intoxication, obviated. This paper deals with only those procedures alleged to be most useful in differentiating the jaundice due to infectious, toxic hepatitis (medical) and that of common duct obstruction (surgical).

In studying these problems there is no laboratory test or combination of tests which can take the place of a careful history, physical examination, and routine observations of chart, blood counts and smears, urines and stools. Lahey's (1) modification of Courvoisier's law is worth alluding to in this respect: "In the presence of jaundice which is painless and progressive and associated with consistently acholic stools, a dilated gall bladder palpable through the abdominal wall is almost certain to be due to malignancy of the head of the pancreas or the lower end of the common duct." Thus simply by the use of sight and touch it is possible to decide the diagnosis. The cataloging of significant points in the histories of 235 cases of jaundice by Flood (2), Seegal, *et al* has shown that revision is needed in the commonly accepted teaching that cancer of the head of the pancreas causes painless jaundice. They found a high incidence of pain as the earliest symptom. Scrutiny of ten times as many cases might supply ten additional important facts to serve clinical judgment. Even then, however, certain decisions could be facilitated by special laboratory evidence.

LABORATORY AIDS

There are five laboratory procedures which have been especially stressed in the literature as having distinct value in the differential diagnosis of intrahepatic jaundice and extrahepatic (obstructive) jaundice: the qualitative van den Bergh reaction, the galactose tolerance test, the urobilinogen determination, the duodenal tube drainage and the study of blood choles-

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terol. I do not discuss flat X-ray plate of the gall bladder region, because by showing a stone, that examination can simply refine the diagnosis of obstruction.

(1) *The Qualitative van den Bergh Reaction:* The history of this test has been summarized by Rabinowitch (3); the technic, by Elton (4). The bio-chemical mechanism involved has not yet been established. In interpreting the test according to van den Bergh and McNee, a direct immediate reaction means obstructive jaundice; a biphasic reaction denotes the jaundice of hepatitis; and a delayed reaction means hemolytic jaundice.

In 1930 Snider and Reinhold (5) felt there was no valid theoretical basis for the use of the van den Bergh reaction in identifying the various types of jaundice. The next year Rabinowitch (3) wrote that the different reactions did not yield the information attributed to them and offered the explanation that pure obstruction and pure hepatitis are rare. Cantarow (6) observed that the varying responses of the test at different times in the same individual tended to discredit its value in differential diagnosis. Some use was accorded the test by Flood, Seegal (2), *et al* in differentiating hemolytic from non-hemolytic jaundice; but none, in the differential of obstructive and hepatic jaundice. By and large, present day investigators (7, 8) frown upon the value of the qualitative van den Bergh reaction.

(2) *The Galactose Tolerance Test:* Davies (8) gives an historical account of this test and describes his technic of giving the sugar and following the blood levels. Roe and Schwartzman (9) use a similar technic but vary their doses according to body weight. Jankelson and Lerner (10) give the galactose intravenously, instead of orally, and follow the non-fermentable fraction of the blood sugar curve as an index of galactose utilization. Most workers (Shay and Schloss (11); Banks, Sprague and Snell (12); Schiff and Senior (13); Rosenberg (14)) adhere to the principles first set down by Bauer in 1906.

The value of this test is said (11) to lie in the fact that all the galactose which fails to be utilized by the liver is eliminated in the urine. Thus in the early presence of jaundice if more than 3 grams are recovered, diffuse liver damage is postulated, and a toxic or infectious type of jaundice is thereby identified. On the other hand, excretion of less than 3 grams is normal and an indication that the etiology of early jaundice is either obstruction or hemolysis. Schiff and Senior (13) applied the test in 100 cases and concluded that it was of great value in differentiating acute toxic or infectious jaundice from the obstructive type. Rosenberg (14) obtained normal (negative) results in all his 16 cases of obstructive jaundice and commented favorably on the value of the test. Clute (15) remarks that the test is simply confirmatory but settles nothing. Banks, Sprague and Snell (12) studied 127 selected cases of jaundice including the two groups under discussion here. They concluded that the galactose test does not uniformly distinguish between obstructive and intra-hepatic types of jaundice, though it may furnish valuable corroborative data in doubtful cases. Their records show clear cut examples in which excessive galactose was excreted (positive tests) in obstruction cases of relatively short duration (4 to 14 days). Shay (13)* answered for these unfavorable results by saying that the tests were not done early enough and that some of the cases perhaps had infection in the biliary tract. Rosenberg (14) suggested that Banks *et al* might have made more accurate use of the test by combining it with the urobilinogen test. Davies (8) and Mann (13)* also advocate the employing of various tests to settle a differential diagnosis.

(3) *The Urobilinogen Determination:* Value of the Urobilinogen test in diagnosis was demonstrated about 50 years ago by Friedrick Müller. He observed that no urobilinogen was present in the urine of a patient with complete biliary obstruction. Thereupon he gave large amounts of bile by mouth and within 48 hours obtained positive urinary tests for urobilinogen.

During the next 40 years the test was refined and the mechanism of urobilinogen production was investigated.

Ten years ago (June, 1925) Wallace and Diamond (16) employed the newer knowledge and reported their studies of 1200 cases, thereby giving prominence to the test. They outlined the rationale and technic of the procedure and gave experimental evidence to support their views which have been generally accepted ever since. Briefly, they asserted that urobilinogen is derived from bilirubin in the intestine, is absorbed from the intestine, and is normally excreted mostly by the liver but also in small amounts by the kidneys. If diffuse liver damage is present, the excretion through the biliary channel is impaired and excessive amounts are put out in the urine. If obstruction to the flow of bile into the duodenum is complete, urobilinogen is non-existent. The authors mention two exceptions to the latter statement. First, in the presence of cholangeitis, bilirubin may be reduced in the infected bile ducts to urobilinogen. Second, small amounts of bilirubin may be excreted from the general circulation into the intestines where urobilinogen will then form. Davies (8), Rabinowitch (3), Rosenberg (14), and Clute (15) record experiences with the urobilinogen test similar to those of Wallace and Diamond.

If biliary obstruction is only partial or if regeneration has had time to develop in a diseased liver, then manifestly the urobilinogen test loses significance. In neither instance will it be consistently positive or negative. Attempts have been made to increase the value of the test in the more difficult differential diagnoses by combining it systematically with other tests. Thus, Rabinowitch (3) feels that the urobilinogen test in conjunction with the qualitative van den Bergh gives more exact information. Rosenberg (14) suggests that the combination of the galactose tolerance and the urobilinogen tests is useful, but that of the two used alone the urobilinogen is the more reliable for differential purposes.

(4) *Duodenal Tube Drainage:* The various types of duodenal tube have been described by Twiss (17, 18), who has also given detailed account of their use. Part of the routine examination in the Gall Bladder Clinic at the New York Post Graduate Hospital (18) is the microscopic, chemical, and bacteriological analyses of the bile fractions recovered from the duodenum. Lahey (1) has emphasized the value of these diagnostic measures especially in distinguishing catarrhal jaundice from obstructive jaundice due to gall stones. The presence of mucus and pus in thin bile argues for the former. Whereas cholesterol crystals bespeak stone. Whole blood may mean carcinoma. Clute (15) of the Lahey Clinic considers duodenal drainage for diagnostic purposes "perhaps the most satisfactory and dependable laboratory test for determining the cause of jaundice" and mentions a series of 30 correct diagnoses to a single mistaken one made by this means.

Duodenal drainage has been employed chiefly for establishing the presence of gall stones. In 1928, Piersol, Bockus and Shay (20) were thereby able to make preoperative diagnoses of stone in 47% of their cases. Three years later Bockus, Shay, Willard and Pessel (21) made accurate diagnoses in 83% of their cases. They assert that the combination of cholesterol crystals and calcium bilirubinate crystals is pathognomonic of gall stones. It is apparently as important to study bile in diagnosing hepato-biliary disease as urine in renal-ureteral disease.

(5) *Blood Cholesterol:* In 1927 Davies (8) wrote that the blood cholesterol level is an important aid in the differential diagnosis of jaundice. An amount of 180 mg % or more, he said, points to obstructive jaundice. Epstein (22) has done pioneer work in this direction and gathered

*See Discussion.

TABLE I

Medical Cases

Case	Age sex	Final diagnosis	How established	Icterus index	van den Bergh	Urobilinogen	Duration Jaundice before tests
1.	43M.	Portal Cirrhosis (Alcoholic)	Clinically	37	D.IM.*	++++	2 wks.
2.	51F.	(Alcoholic)	Autopsy	120	D.IM.	+++	2 wks.
3.	57M.	(Alcoholic)	Clinically	46	D.IM.	++++	Few wks.
4.	61M.	(Alcoholic)	Clinically	47	D.IM.	Neg.	5 wks.
5.	56M.	(Alcoholic)	Autopsy	26	D.IM.	++++	5 days
6.	50M.	(Alcoholic)	Clinically	13	D.D.	++++	?
7.	52F.	(Alcoholic)	Clinically	20	D.IM.	+++	?
8.	62M.	(Alcoholic)	Clinically	++++		Neg.	7 wks.
9.	52M.	(Alcoholic)	Clinically	+		++++	?
10.	53F.	(Alcoholic)	Clinically	15	D.D.	Neg.	1 mo.
11.	24F.	(Alcoholic)	Autopsy	43	D.IM.	+	2 wks.
12.	48M.	(Alcoholic)	Clinically	12	D.D.	++++	?
13.	37M.	(Alcoholic)	Clinically	112	D.IM.	Neg.	4 days
14.	58M.	Portal Cirrhosis (Non-Alcoholic)	Clinically	43	D.IM.	+	4 mos.
15.	63M.	(Non-Alcoholic)	Clinically	55	D.IM.	Neg.	10 days
16.	49M.	Cirrhosis with Multiple liver abscesses	Operation	75	D.IM.	Neg.	5 days
17.	44M.	Biliary Cirrhosis	Clinically	37	D.IM.	Neg.	3 yrs.
18.	22F.	Catarrhal Jaundice	Clinically	++++		++++	4 days
19.	23F.	Catarrhal Jaundice	Clinically	22	D.IM.	+	2 wks
20.	44F.	Catarrhal Jaundice	Clinically	90	D.IM.	Neg.	1 wk.
21.	16M.	Catarrhal Jaundice	Clinically	25	D.D.	++++	1 wk.
22.	61M.	Catarrhal Jaundice	Clinically	49	D.IM.	Neg.	10 days
23.	49F.	Catarrhal Jaundice	Clinically	22	D.IM.	++++	2 wks.
24.	32F.	Catarrhal Jaundice	Clinically	60	D.IM.	Neg.	3 days
25.	38F.	Acute Toxic Hepatitis	Autopsy	45	D.IM.	++++	5 wks.
26.	23M.	Acute Toxic Hepatitis	Clinically	10	D.D.	++++	?
27.	41F.	Hepatitis	Clinically	33	D.IM.	Neg.	1 wk.

*D.IM. Represents direct immediate.
D.D. Represents direct delayed.

evidence to show that a pronounced reduction in the blood cholesterol level indicates parenchymatous disease of the liver, whereas hypercholesteremia denotes an obstructive lesion. Lehnherr (23) records similar experiences with lipid analyses in studying the causes of jaundice. However, his results seem to differ from Epstein's in certain details to do with the free-cholesterol: ester-cholesterol ratios in obstructive jaundice. Such discrepancies simply mean that this work is in its infancy.

CLINICAL STUDY

Although in recent years there has been no special or organized study made of jaundice at the Milwaukee County General Hospital, still certain jaundiced patients have submitted to a wide variety of laboratory tests for diagnostic and prognostic purposes. I have been particularly interested in studying the records of a group of 50 patients who received among other tests the combination of the qualitative direct van den Bergh and urobilinogen determinations. It has seemed desirable to appraise the value of these casual observations.

AUTHOR'S STUDY

The 50 cases under consideration were arbitrarily divided into 27 medical and 23 surgical on the basis of the site of lesion. Those with primary liver disease were considered medical; and those with extra hepatic biliary conditions, surgical. Tables I and II show the details of this grouping.

As intimated in the first paragraph, the special interest of this study is in tests which may expedite early diagnoses. Hence I have recorded only the first results, which were obtained shortly after admission in nearly every instance. The "duration of jaundice" pertains to the period from onset to the initial tests.

The pertinent results of this survey are summarized in Table III. It is interesting to note that in these two heterogeneous groups the figures run approximately parallel. Hence, it would seem that single urobilinogen or van den Bergh determinations can not be expected to help in differentiating medical from surgical jaundice. Further study will be made on the value of repeated tests.

There are not enough cases of any given type within the groups to judge the merits of these tests in distinguishing certain syndromes. Nevertheless, there are indications that even within narrower limits there is nothing specific about these tests. The similarity between cases 3 and 4 of the portal cirrhosis type is striking. The ages of the patients, the depth and duration of jaundice were approximately the same.

TABLE II

Surgical Cases

Case	Age sex	Final diagnosis	How established	Icterus index	van den Bergh	Urobilinogen	Duration jaundice before tests
1.	61F.	Biliary Cirrhosis, stone in common duct	Autopsy	34	D.IM.*	Neg.	4 yrs.
2.	46F.	Biliary Cirrhosis, stone in common duct	Clinically	21	D.IM.	+	4 wks
3.	58F.	Post Op. Stricture of common duct	Clinically	63	D.IM.	Neg.	5 yrs.
4.	33F.	Stones with Cholangeitis	Operation	30	D.IM.	+	6 days
5.	58M.	Obstruct. Jaundice. ? Ca. head pancreas	Operation	72	D.IM.	Neg.	3 wks.
6.	58M.	Gall Stones	Clinically	6		+	1 day
7.	28F.	Gall Stones	Operation	36	D IM.	+	4 days
8.	67F.	Stones in common duct	Operation	+		+++	1 wk.
9.	64F.	Stone in common duct	Operation	27	D.IM.	Neg.	10 days
10.	74M.	Ca. head pancreas	Clinically	30	D.IM.	+++	1 wk.
11.	75M.	Ca. head pancreas	Clinically	75	D.IM.	Neg.	3 wks.
12.	53M.	Ca. head pancreas	Operation	50	D.IM.	Neg.	2 wks.
13.	54M.	Metastatic Ca. (Proved Ca. Stomach)	Clinically	60	Neg.	Neg.	4 mos.
14.	49M.	Metastatic Ca. (Proved Ca. Stomach)	Clinically	++		+	10 days
15.	68F.	Cholecystitis with Cholelithiasis	Clinically	70	D.IM.	Neg.	4 days
16.	71F.	Cholecystitis with Cholelithiasis	Clinically	+		++	3 days
17.	47F.	Cholecystitis with Cholelithiasis	Operation	15	D.D.	+	1 wk.
18.	61F.	Cholecystitis with Cholelithiasis	Clinically	14	D.D.	Neg.	1 mo.
19.	47F.	Cholecystitis with Cholelithiasis	Clinically	+		++++	3 wks.
20.	59M.	Cholecystitis with Cholelithiasis	Autopsy	19	D.D.	++++	4 days
21.	58M.	Cholecystitis with Cholelithiasis	Clinically	+		Neg.	1 wk.
22.	57F.	Acute Cholecystitis	Clinically	+		++++	3 days
23.	50F.	Acute Cholecystitis	Clinically	15	D D.	++++	1 wk.

*D.IM. Represents direct immediate.
D.D. Represents direct delayed.

The sex and van den Bergh reaction were identical. Yet one gave a markedly positive urobilinogen reaction; and the other, a flat negative. It has been said that early in catarrhal jaundice the urobilinogen test is most likely to be positive. Cases 20 and 21 were examined one week after the onset. One proved negative; the other, positive. The van den Bergh reactions also differed. Cases 10 and 11 with probable cancer of the head of the pancreas, and cases 18 and 19 with gall bladder disease afford further example of discrepancies in the urobilinogen testing of clinically similar material.

TABLE III

	Surgical	Medical
Total positive urobilinogens	13	16
Total negative urobilinogens	10	11
Per cent positive	56.5%	59.2%
Total van den Berghs done	16	24
Direct immediate	11	19
Delayed direct	4	5
Negative	1	0
Per cent direct immediate	68.7%	79.1%

In conclusion, it appears from the above study that isolated urobilinogen and qualitative direct van den Bergh tests do not with any regularity help distinguish the jaundice of medical origin from that due to a surgical lesion. This statement is made, of course, from a statistical point of view. It is only fair to state in addition that the records show certain individual instances in which the urobilinogen test when repeatedly negative has proved to be of definite value in helping to decide whether or not to operate on a jaundiced patient.

SUMMARY

1. Attention is called to the desirability of making early differential diagnoses between "medical" and "surgical" jaundice.

2. In this respect, the importance of bedside observations is stressed.

3. The five most popular laboratory tests for differential purposes are appraised in varying detail.

4. A series of 50 cases is presented in chart form to show especially the value of single urobilinogen and qualitative direct van den Bergh tests in distinguishing "medical" and "surgical" jaundice.

5. The figures indicate that no significant information can be expected from these laboratory procedures on the basis of single observations only.

I wish to acknowledge the generosity of Dr. Francis D. Murphy, Medical Director of the Milwaukee County General Hospital, who suggested this subject and gave me access to the clinical records.

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SECTION II—*Experimental Physiology*

An Improved Gastric Test Meal*

By

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STUDIES on gastric secretion are to a certain extent handicapped and limited because of the lack of a standard test meal. The more commonly used clinical test meals (shredded wheat biscuits, arrow root cookies, bread or toast, with water or weak tea) have frequently been justly criticized because of their very low secretogogue effect which renders them inadequate tests of the acid secreting power of the stomach. This generally recognized failure of the usual test meals has led to the wide spread use of histamine, the alcohol test meal or the meat and water test meal.

Histamine is undoubtedly a powerful stimulant for hydrochloric acid secretion, but recent investigations have shown that its action is to some extent abnormal since it appears to stimulate solely the secretion of hydrochloric acid and not that of pepsin and other organic constituents. We have recently shown (1) that histamine may mask certain regulatory phenomena which are seen when meat extracts are used and have concluded that histamine is either qualitatively or quantitatively different from the naturally occurring secretogogues present in meat. The alcohol test meal is too abnormal to be seriously considered. The use of the meat and water test meal, especially in experimental work, is becoming increasingly popular. From the standpoint of a normal, adequate stimulus for gastric secretion it is undoubtedly highly satisfactory but it presents certain very serious analytical difficulties which render the results of doubtful validity. The presence of a high concentration of powerful buffer substances render accurate titration almost impossible. In addition, the acid and alkali combining power of the meat are undergoing constant alterations during the course of the test, due to digestion and liberation of protein digestion products. The assumption that the titration values obtained during the course of the test meal represent hydrochloric acid secreted by the stomach is, to say the least, highly questionable.

In none of the commonly used test meals is it possible to evaluate the factor of dilution of the gastric secretion by the fluid of the test meal; that is, in a given gastric sample it is not possible to determine what per cent of the sample is fluid originally given

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with the test meal and what per cent is the fluid of the secretions entering the stomach. Because of this it is impossible to determine the true composition of the gastric secretions. An extreme hypothetical example will illustrate the importance of the factor of dilution of the gastric secretions by fluid of the test meal. Suppose that two subjects are given the same test meal which contains 200 c.c. of fluid and that both subjects secrete exactly the same amount of acid of exactly the same strength during the test period. Suppose however that the gastric sample removed from subject A consists of 100 c.c. of fluid from the test meal plus the secreted hydrochloric acid, while from subject B it consists of 50 c.c. of fluid from the test meal plus the secreted acid. Titration of the gastric samples would lead to the erroneous conclusion that subject A secreted only half as much acid as subject B, whereas in reality the amount of acid secreted was the same, the difference being that in one instance it was diluted by 100 c.c. and in the other by 50 c.c. of fluid from the test meal. Gorham (2) pointed out this fallacy and suggested the use of phenolsulphonphthalein (phenol red) in the test meal in order to correct for dilution of the gastric secretions. In a large series of gastric analyses he illustrated the striking difference that may exist between corrected and uncorrected values. In our previous studies on the regulation of gastric acidity we have used phenol red in the test meal and have shown its great value (1, 3, 4, 5, 6, 7).

From the above considerations it follows that an ideal gastric test meal should have the following qualifications: (1) Its secretogogue effect should be high and act through normal channels so that it will be unnecessary to use histamine or other extraneous stimulants. (2) It should be relatively low in organic material and buffer substances in order to allow accurate titration. (3) It should not undergo marked changes in consistency while in the stomach. (4) It must be possible to use phenol red in order to determine the true composition of the secretions entering the stomach. (5) It must be possible to remove pigments, mucus and other interferring substances which might render the colorimetric determination of the per cent of phenol red inaccurate due to foreign color or turbidity. Phenol red must not be removed with these interferring substances. (6) It must be a liquid meal so that phenol red is not adsorbed by solid particles. (7) It must be possible to standardize the test meal, before use, with regard to its content of titratable acid. (8) The meal should have no acid neutralizing or combining power.

In attempting to develop a test meal having the above qualifications, several substances (milk, whey, Armour's meal extract) were tried but, for various reasons, found unsatisfactory. Armour's meat extract was discarded because of the extreme variability in its secretogogue content. Liebig's meat extract (Lemco brand) was found to be quite constant in secretogogue effect and a two per cent solution was found to exert a marked and maintained stimulation of gastric secretion. Since the secretogogues present in Liebig's extract are a concentrated preparation of those normally occurring in meat, it appears that the stimulating effect can be considered to be quite normal in mode of action.

A study of simple, unmodified aqueous (2 per cent) solutions of Liebig's extract showed that where a high degree of accuracy is desired, they are not satisfactory for the following reasons: (1) When slowly acidified with tenth normal hydrochloric acid a degree of acidity is finally reached at which a heavy flocculent precipitate settles out, further addition of acid redissolves the precipitate. A cursory study of this phenomenon suggested that when the precipitate forms there is an exchange of base with neutralization of some of the hydrochloric acid. (2) Aqueous solutions possess a variable ability to combine with and neutralize hydrochloric acid. (3) Non volatile acids are present. These would not interfere with the usual clinical analysis involving only titration, provided that the meal was titrated before using. They would however interfere with the accurate determination of neutral chloride in the gastric samples, a determination which is often of importance in experimental studies.

Because of the above findings it was necessary to prepare a two per cent solution of Liebig's extract in which these undesirable features were eliminated in the following general manner: First, to remove the material precipitated by acid. Second, to supply sufficient base to care for the non volatile acids. Third, to leave the solution slightly acid with hydrochloric acid so that its acid neutralizing and combining powers would be saturated.

Preparation of Two Liters of Two Per Cent Liebig's Extract Test Meal Containing 15 mgm. of Phenol Red per Liter

(1) 40 grams of Liebig's extract are dissolved in one liter of distilled water. The water may be warmed to facilitate solution but should never approach the boiling point since this may destroy the secretogogue.

(2) Add 30 mgm. of the sodium salt of phenol red.[1]

(3) Add 20 c.c. of 20 per cent sodium carbonate solution. After addition the solution should be definitely alkaline as shown by the red color of the phenol red.

(4) Add slowly with constant stirring one liter of tenth normal hydrochloric acid. After addition the solution should be acid to litmus paper.

(5) Let stand until a heavy flocculent precipitate settles out.

(6) Filter. The first portions to pass through the filter may be turbid and should be returned until the filtrate is crystal clear.

Since the meal keeps well with proper refrigeration, a sufficient quantity for one or two weeks work can be prepared at one time. The taste is pleasant being practically that of beef extract, hence it can be taken by mouth. When titrated as described below, the acidity of various batches of the meal will vary from 11 to 22 c.c. of tenth normal acid per 100 c.c.. If values above 22 c.c. of tenth normal acid are obtained alkali should be added to reduce the acidity to within the above range. This degree of acidity has no influence on acid secretion or duodenal regurgitation (1).

The amount of meal administered will depend upon the length of time that it is desired to follow the acidity curve and the number of samples taken. In experiments on dogs we have administered from 600 c.c. to 900 c.c., depending upon the size of the animal and the emptying time of the stomach. Samples (30

1. We have used the dry, powdered phenol red and dissolved the 30 mgm. in 33 c.c. of N/10 NaOH. The amount of alkali used should be kept constant since it is a factor in determining the final acidity of the meal.

c.c.) were removed every half hour until the stomach emptied which required from 1½ to 2½ hours.

METHODS OF ANALYSIS

The analysis consists of two procedures. (A) Titration of the test meal before use and of the samples removed from the stomach. (B) Determination of the per cent of phenol red in the samples removed from the stomach.

(A) *Titration of the Test Meal and of the Gastric Samples*

In previously reported studies on the regulation of gastric acidity we determined the total chloride, neutral chloride and by difference the acid chloride in the test meal and the gastric samples. While this method is highly accurate it is unnecessarily complicated for clinical use. We attempted to work out a method of titrating the total acid which would be in reasonably good agreement with the acid chloride as determined. When phenolphthalein was used as an indicator it was found that the results were much too high and very irregular. Several other indicators were tried and brom cresol purple was found to give results in satisfactory agreement with the acid chloride determinations.

The method of titration is as follows:

A five c.c. centrifuged sample of gastric contents or an uncentrifuged sample of original test meal is diluted with 75 c.c. of distilled water and placed on top of a water bath for 30 minutes. Six drops of brom cresol purple (0.4 per cent in 95 per cent alcohol) are added. The titration is performed on the steaming sample using twentieth normal sodium hydroxide. The result is expressed as c.c. of tenth normal acid per 100 c.c. of gastric sample or test meal. As the alkali is added the color of the solution first becomes a greenish yellow, next a light purple mixed with reddish brown; as more alkali is added this color at first darkens but finally changes to a rich wine colored purple free from reddish brown. The latter is taken as the end point. With practice the end point is easily recognized. The dilution with water and warming are important aids in reducing the effect of buffer substances and producing a sharp end point.

The titration value thus obtained is for total acid. We have not attempted to determine free and combined acid because of the doubtful character of these values (8, 9) and also because it is believed that sufficient information can be obtained from the total acid figure.

A sample of the test meal should be titrated each time that a test is performed.

(B) *Determination of the Per Cent of Phenol Red in the Gastric Samples*

In this determination a sample of the original test meal is used as the standard.

(1) Five c.c. samples of the original test meal and of each of the gastric samples are placed in 15 c.c. centrifuge tubes. (2) Add 2 c.c. of 20 per cent sodium tungstate to each. Mixing is not necessary. Due to the alkalinity of the sodium tungstate the samples turn a reddish color. (3) Add 2 c.c. of 1.33 normal sulfuric acid[2] and mix by inverting several times. Do not shake. (4) Stopper tubes and allow to stand for from 1 to 1½ hours. A flocculent precipitate settles out usually leaving a clear supernatant fluid. The prolonged period of standing is not always necessary but aids materially in clearing the samples when the dilution is great or large amounts of duodenal secretions are present. (5) Centrifuge at high speed for 10 minutes and decant the supernatant fluid into dry 15 c.c. graduated centrifuge tubes. (6) Reduce the volume in all tubes to 8 c.c. and alkalinize by adding to each 1 c.c. of approximately 20 per cent sodium hydroxide (5 c.c. of saturated sodium hydroxide plus 10 c.c. of water). (7) Mix by inverting several times and centrifuge for 10 minutes. (8) Compare the gastric samples with the sample of the original test meal in a colorimeter and determine the per cent of phenol red present. It is best to set the standard at 5 m.m. and make the comparison on this basis.

Immediately after alkalinization the samples turn a purplish red color different from the true color of alkaline phenol red. This is due to certain substances in the Liebig's extract which react with the excess tungstate, in an alkaline media, to produce a blue color. This color fades rapidly and is also absorbed by the small precipitate thrown down and is gone at the end of the 10 minute centrifuging, leaving the true alkaline phenol red color.

If the dilution of the gastric sample has been very great or large amounts of duodenal contents are present, it frequently happens that the treatment with sodium tungstate and sulfuric acid does not yield a perfectly clear supernatant fluid but a milky one which cannot be cleared by centrifuging. Such samples will clear after addition of the alkali and are suitable for comparison.

When large amounts of bile, especially gall bladder bile are present in the gastric sample, the color after alkalinization is often faintly tinged with yellow instead of being the pure alkaline phenol red color. This color can be almost perfectly matched by adding a small amount of picric acid to the standard. The method is as follows: To about 4 c.c. of standard add 4 to 5 *very* small crystals of picric acid and shake until dissolved. By mixing varying amounts of the picric standard with the untreated standard a yellowish tinge can be produced which matches that of the gastric sample. It has not been necessary to use this measure on many normal dogs but it may often be necessary after gastroenterostomy or Polya types of operations.

When an experiment is continued until complete emptying of the stomach occurs it is usually found that the last samples are too dilute to determine the per cent of phenol red accurately. We have routinely accurately diluted such samples with equal parts of the original test meal and made the determination of the per cent of phenol red on the diluted sample. A simple correction[3] gives the per cent of phenol red in the original undiluted sample. With few exceptions we have diluted all samples beginning at 1½ hours. If one uses a greater amount of phenol red in the test meal in order to have sufficient color for the final sample then it is found that the color is too deep for accurate comparison in the early samples. The dilution method has been found very satisfactory.

Bile. If bile is to be tested for in the gastric samples a Pettenkoffer ring test should be used. The meal does not give false positive reactions.

CALCULATIONS

The general principle of the calculation is as follows: while the test meal is in the stomach various fluid secretions are mixed with it. These secretions dilute the test meal and lower the per cent of phenol red. The decrease in the per cent of phenol red in the samples removed from the stomach shows the cubic centimeters of secretions mixed with each 100 c.c. of the sample. If the fluid which diluted the test meal had been a neutral fluid containing neither acid or alkali, then the acid in the test meal would be lowered by dilution to the same extent as the phenol red, hence the acid would be equal to the amount in the original test meal corrected for dilution (multiplied by the per cent of phenol red in the gastric sample). However, if the fluid which diluted the test meal contained acid, the acid added would be the difference between the acid

2. 35 grams of concentrated sulfuric acid diluted to 500 c.c. with distilled water is sufficiently accurate and can be used without further standardization.

3. The per cent of phenol red in the diluted sample minus 50 x 2 gives the per cent of phenol red in the original undiluted sample.

TABLE I

A series of fractional gastric analyses performed on normal dogs

Test Meal c.c. N/10 Acid per 100 c.c.	*Gastric Sample* c.c. N/10 per 100 c.c.	P. S. P. percent	Acid in Test Meal Corrected for dilution	Extra Acid. c.c. N/10 per 100 c.c.	*Acid Concentration of Gastric secretion.* c.c. N/10 per 100 c.c.	Total Fluid	Acid Fluid	Non Acid Fluid	Percent Acid Fluid	Bile	Time Hours	Type Curve
19	26	89	17	9	82	11	5	6	45	0	½	I
	43	75	14	29	116	25	17	8	68	+	1	
	55	50	10	45	90	50	27	23	54	+++	1½	
17	25	89	15	10	91	11	6	5	55	0	½	I
	37	78	13	24	109	22	14	8	64	+	1	
	42	38	6	36	58	62	21	41	34	+++	1½	
	42	30	5	37	53	70	22	48	31	+++	2	
12	19	91	11	8	89	9	5	4	56	0	½	I
	31	82	10	21	117	18	12	6	67	++	1	
	48	68	8	40	125	32	24	8	75	++++	1½	
	67	50	6	61	122	50	36	14	72	+++	2	
	62	36	4	58	91	64	34	30	53	++++	2½	
12	16	94	11	5	83	6	3	3	50	0	½	I
	34	82	10	24	133	18	14	4	78	0	1	
	48	67	8	40	121	33	24	9	73	+	1½	
	56	52	6	50	104	48	30	18	62	++	2	
	59	32	4	55	81	68	32	36	47	+++	2½	
13	21	88	11	10	83	12	6	6	50	0	½	II
	32	79	10	22	105	21	13	8	62	++	1	
	50	56	7	43	98	44	25	19	57	+++	1½	
	63	50	7	56	112	50	33	17	66	+++	2	
15	19	88	13	6	50	12	4	8	33	0	½	II
	31	83	12	19	112	17	11	6	65	trace	1	
	40	50	8	32	64	50	19	31	38	++	1½	
	57	36	5	52	81	64	31	33	48	++	2	
12	15	94	11	4	67	6	2	4	33	0	½	III
	31	76	9	22	92	24	13	11	54	++	1	
	50	52	6	44	92	48	26	22	54	+++	1½	
13	18	88	11	7	58	12	4	8	33	0	½	III
	31	71	9	22	76	29	13	16	45	0	1	
	42	44	6	36	64	56	21	35	38	+	1½	
	54	34	4	50	76	66	29	37	44	+	2	
11	19	91	10	9	100	9	5	4	56	0	½	IV
	34	79	9	25	119	21	15	6	71	0	1	
	48	71	8	40	138	29	24	5	83	+	1½	
	60	62	7	53	139	38	31	7	82	++	2	
	82	44	4	78	139	56	46	10	82	++	2½	
11	19	93	10	9	129	7	5	2	72	0	½	V
	33	83	9	24	141	17	14	3	82	0	1	
	46	77	8	38	165	23	22	1	96	0	1½	
	59	70	8	51	170	30	30	0	100	trace	2	
	73	62	7	67	176	38	39	0	100	+	2½	

in the original test meal, (corrected for dilution) and the acid in the gastric sample. If the secretions which diluted the test meal contained no acid (total anacidity) then the acid in the gastric sample would be less than that in the original test meal (corrected for dilution) due to neutralization of some of the acid of the test meal. The details are as follows:[4]

(1) *Cubic Centimeters of tenth normal acid secreted*

The c.c. of tenth normal acid in the original test meal multiplied by the per cent of phenol red in the gastric sample, corrects the original test meal for dilution. If the acidity of the gastric sample is greater than this the difference will represent the c.c. of tenth normal acid secreted by the stomach.

Example:

Test meal contains 12 c.c. of N/10 acid per 100 c.c.

Gastric sample contains 48 c.c. N/10 acid per 100 c.c. and 67 per cent phenol red.

12 x 67 per cent = 8 c.c. (correction of test meal for dilution).

48 — 8 = 40 c.c. N/10 acid secreted by stomach.

In total anacidity the acid in the gastric sample may be less than that in the test meal corrected for dilution. The difference represents the acid of the test meal which was neutralized by the mildly alkaline secretions.

Example:

Test meal contains 12 c.c. of N/10 acid per 100 c.c.

Gastric sample contains 2 c.c. of N/10 acid per 100 c.c. and 80% phenol red.

12 x 80 per cent = 10 c.c. (correction of test meal for dilution).

10 — 2 = 8 c.c. of acid in test meal neutralized.

(2) *The Acid Concentration of the Secretions in the Gastric Sample*

The decrease in the per cent of phenol red in the sample removed from the stomach shows the c.c. of secretion in each 100 c.c. of sample. If the c.c. of extra acid are divided by the c.c. of secretion and multiplied by 100 the result will give the c.c. of N/10 acid per 100 c.c. of secretion.

Example:

Per cent of phenol red in gastric sample = 67, hence 33 c.c. (100 — 67) of secretion entered the stomach and were mixed with each 100 c.c. of the sample.

The c.c. of extra N/10 acid = 40.

40 ÷ 33 = 1.21 x 100 = 121 c.c. of N/10 acid per 100 c.c. of secretion in the sample.

A further calculation which has been found of value in studying the results of a gastric analysis is the division of the total fluid secretions entering the stomach into the *acid fluid* and the *non-acid* fluid.

1. *The Total Fluid (Secretion)* entering the stomach is shown by the decrease in the per cent of phenol red.

2. *The Acid Fluid.* The work of several recent investigators (3, 10, 11, 12, 13, 14, 15, 16, 17, 18) has agreed in

4. In the calculations it is unnecessary to use fractions of cubic centimeters. All figures are rounded off to the nearest whole number.

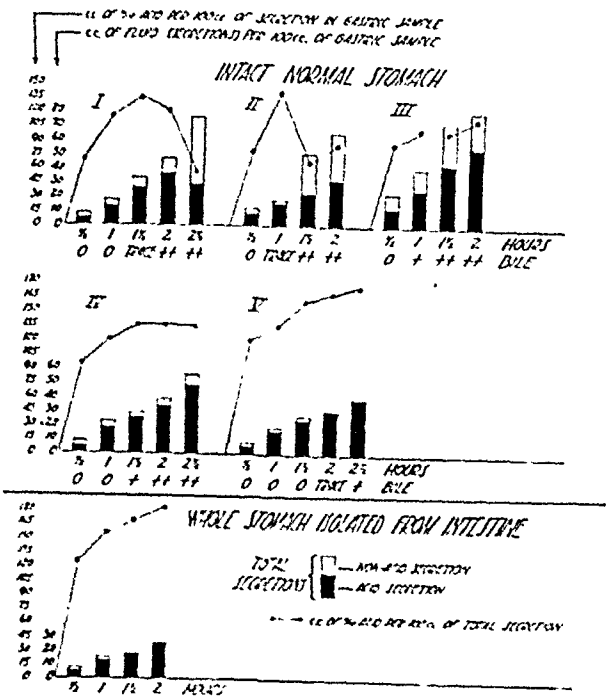


Fig. 1

1. UPPER HALF. The 5 types of Acidity Curves obtained in 67 experiments on 11 normal dogs.
2. LOWER HALF. An average curve constructed from 10 fractional gastric analyses performed on four whole stomach pouches.

showing that the pure acid secretion of the fundic glands is isotonic with the blood and that the strength at which it is secreted remains approximately constant regardless of the rate of secretion and is unaltered by the acidity of the gastric contents. All of the above investigators have obtained approximately the same value for the strength of the pure acid secretion but the most accurate value is that of Hollander (11) who has shown that the pure acid secretion remains constant at 0.170 normal (604 mgm. of acid chloride per 100 c.c.). Because of the constancy of this value it is possible to determine the fluid of the acid secretion. This is done by dividing the c.c. of extra N/10 acid by 1.7.

Example:

The gastric sample is found to contain 40 c.c. of extra N/10 acid per 100 c.c.

40 ÷ 1.7 = 24 c.c. of acid fluid. This value of course represents the acid which was secreted and not neutralized.

3. *The Non-Acid Fluid* is the difference between the *total* and the *acid* fluid. The non acid fluid consists of several secretions in varying amounts and includes, the mucus and mucoid secretions of the pyloric and fundic regions, the regurgitated duodenal secretions and the fluid of acid which was secreted and subsequently neutralized.

The acid concentration of the total fluid entering the stomach is determined by the relative amounts of acid and non acid fluids, the higher the per cent of acid fluid the higher the acid concentration of the total fluid. It is, therefore, often helpful to determine the per cent of acid fluid in the total fluid secretions entering the stomach.

Several complete analyses are shown in Table I.

In the lower half of Figure 1 is shown an average curve constructed from 10 fractional gastric analyses done on four whole stomach pouches. It is seen that the non acid fluid gradually becomes smaller in amount and may finally disappear, hence the acid concentration of the total secretions may reach very high values. This is due to two factors. First the non acid fluid of intragastric origin is small in amount (5) and second, absorption of non acid fluid (water) occurs (19).

In a series of 67 experiments on 11 normal dogs we were able to recognize 5 types of curves which are shown in the upper half of Figure 1. The frequency of these different types was as follows:

Type I	42 or 63 per cent
Type II	12 or 19 per cent
Type III	7 or 10 per cent
Type IV	3 or 4 per cent
Type V	3 or 4 per cent

Types I, II and III comprise 92 per cent of the total number. In these it is seen that there is an abrupt increase in non acid fluid near the end of the curve just before emptying occurs. When these curves are compared with the average curve obtained in the whole stomach isolated from the duodenum, it is evident that the increase in non acid fluid is due to regurgitation of duodenal secretions. Curves of types IV and V are not due solely to lessened duodenal regurgitation but also to absorption of non acid fluid (water) from the gastric contents. A more detafled discussion of these various types of curves has been given elsewhere (19).

SUMMARY

(1) The preparation and use of a new test meal consisting of two per cent Liebig's extract containing phenol red is described. The advantages of this meal over other commonly used test meals are discussed.

(2) Illustrations of the types of curves obtained on normal dogs are given and compared with curves obtained on while stomach pouches isolated from the duodenum. This comparison shows the importance of duodenal regurgitation in determining the type of curve.

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SECTION III—*Nutrition*

Clinical Aspects of Vitamin B-Complex Deficiency in Association with Disease of the Gall Bladder*

Report of an Instance

By

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MANIFESTATIONS of deficiency of one or several components of the vitamin B complex are receiving increasing attention particularly from the standpoint of diagnosis. Cowgill (1) has included the far reaching clinical implications of such deficiency in his discussion of vitamin B requirements of man. Elsom (2, 3) notes characteristic symptoms in her two cases of vitamin B deficiency studied clinically. In addition to loss of weight, anorexia, edema, hypotension and signs of neurological involvement, she notes skin changes, similar to those which occurred in our present case, in certain of her patients. We (4) have noted changes in the color and texture of the skin of the forearms, similar to those in pellagra but without other accompanying symptoms, which occurred in a patient receiving liver extract intramuscularly for pernicious anemia, and interpreted them as related to one or more members of the vitamin B complex.

In the case here reported, certain characteristic symptoms, the history of prolonged dietary insufficiency, the changes in the skin of the hands and forearms, and the response to administration of vitamin B complex, all indicate deficiency of certain of these components. The choleystitis is believed responsible in part for exacerbations of this deficiency. Thus, it is to record an additional clinical aspect of this disease, particularly with regard to its occurrence with and recognition in the presence of cholecystitis, that this case is reported.

REPORT OF CASE

Mrs. T. H. H., a 58 year old white female had experienced attacks of abdominal pain at intervals since their onset fourteen years ago. Nine years ago, because of repeated attacks of abdominal pain, an appendectomy was done, but the attacks of abdominal pain continued and, were "the same kind as before" appendectomy. More recently the attacks had become localized to the right upper quadrant of the abdomen, and symptoms included in addition to the pain, considerable gas with abdominal distention, jaundice upon one occasion and anorexia. A diagnosis of cholecystitis had been made several years ago, based upon these symptoms but there was no operation.

During the spring of 1934, the patient noted the onset of malaise at which time she felt poorly generally, and experienced anorexia and epigastric distress. Her diet during the summer of 1934 accordingly consisted practically entirely of fruits and vegetables, with chicken the only meat and this only upon occasion.

Soon after a period of marked emotional and physical activity, incident to a change in residence, the patient noted on September 18, 1934, together with marked increase in the anorexia, a small red spot in the palm of the left hand. This same type of lesion appeared in a corresponding position on the right hand and upon the right foot about one week later. The lesions at first were red, not raised and were non-pruritic. There was no sore tongue, no edema of the ankles and no diarrhea at this time. The anorexia, marked at the time of onset of the skin lesions, improved during the intervals of freedom from the attacks of gas and abdominal distention, but recurred with exacerbations in the symptoms.

After the skin lesions had spread to involve the entire palmar surface of each hand the patient sought medical advice and the diagnosis of eczema was followed by various kinds of ointments, and X-ray treatments of the hands, but without response.

When first seen, the preceding facts constituted the history, while examination of the hands revealed marked changes. The skin of both palmar surfaces was markedly thickened, dry, scaling and there were many deep furrows present. The skin over the dorsum of either foot was pigmented. During a particularly severe attack which occurred April 17, 1935, when the patient was confined to bed for several days, there was very marked anorexia, vertigo, marked pain in the gall bladder region, and a feeling of lameness and numbness in the right leg, and an increase in depth of pigmentation of the dorsum of either foot. Most striking was the appearance of the ventral surface of the lower third of each forearm and in the

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antecubital fossae. Here there occurred a reddening of the skin which within a period of about ten days took on a brownish hue, the skin in these regions at the same time losing some of its elasticity and becoming studded with fine furrows, an appearance which made the involved skin seem older than the normal skin in the surrounding areas.

Positive findings in the remainder of the physical examination were as follows. The skin over the trunk and remaining portion of the extremities was of good texture and color. The heart was of normal size, rate, rhythm and with normal sounds. Blood pressure was 160/80. Slight tenderness upon palpation of the right upper quadrant of the abdomen was present but the liver and spleen were not palpable. Tendon reflexes were hyperactive.

The urine was clear yellow in color with a faint greenish fluorescence; there was no albumin, no sugar nor formed elements. Erthrocyte and leucocyte counts were normal. Gastric analysis revealed free acid from 8 to 16 units (c.c. N/10 NaOH) and total acidity 16 to 30 units. An oral cholecystogram revealed a non-filling gall bladder, while there was constantly present on the X-ray films a shadow at the site of the gall bladder, three or four times normal size; there were also several small shadows, interpreted as gall stones. Blood cholesterol determinations on May 24th and June 7th were 200 and 228 mgm. per cent respectively.

There was very satisfactory response upon the part of practically all symptoms to vitamin B in the form of brewer's yeast. On June 28, 1935, a cholecystectomy was done at which time a gall bladder containing many stones was removed by Professor Hart at the Duke University Hospital.

The patient has subsequently remained well.

DISCUSSION

The symptoms in our case agree with those reported by Elsom as indicative of deficiency in certain components of the vitamin B complex. Anorexia, one of the earliest symptoms was present practically continually in our patient, while at intervals it became very marked. It was undoubtedly responsible for the choice and limitation of dietary constituents to those substances which were more immediately palatable, but which, having a low vitamin B content, consequently produced an exacerbation of the symptoms.

The diet taken by our patient agrees well with that upon which patients studied by Elsom developed clinically obvious vitamin B deficiency. Characteristically, although it fluctuated in intensity, the neuritis became more severe at the time of exacerbation of the gastro-intestinal and skin symptoms.

The initial skin lesions, in presenting when the anorexia was particularly marked, and consisting of single red non-pruritic spots on the palmer surfaces of the hands and the dorsal surfaces of the feet, as in pellagra, behaved exactly as do similar lesions in experimental animals upon vitamin B deficient diets, and just as did the skin lesions in Elsom's patient (3).

As a manifestation of deficiency disease, there are many aspects of this case which are both of interest and importance for diagnosis and treatment. These are: first, deficiency in members of the vitamin B complex resulting from progressively decreasing intake of these substances in the diet; second, increased demand upon vitamin B substances consequent to the presence of infection; and third, decreased opportunity for absorption of important food materials (vitamin fractions) from the intestinal tract because of vigorous catharsis.

It is well, in the presence of anorexia, particularly if it is progressive, to administer the various vitamin B fractions, because otherwise a vicious circle will result. In the presence of anorexia the diet usually becomes an exclusively carbohydrate one, thus resulting in a markedly lessened vitamin B intake. If we accept Cowgill's contention that the ordinary diet is probably scarcely adequate in vitamin B substances, then the marked ill effects of continued further restriction will be evident.

In the presence of infection, coincident with the increase in general metabolic processes, it is very evident that the demand upon vitamin B substances will be much increased. In many instances the gastro-intestinal symptoms as a manifestation of vitamin B deficiency may be obscured by other etiological factors, but in a case such as the present one, the skin manifestations leave little if any doubt as to the etiological factor. The appearance of the most characteristic skin manifestations, in turn, coincident with a marked increase in the gall bladder infection upon one occasion indicates the increased demand upon vitamin B substances upon such an occasion.

That the increased rate of passage of food through the intestinal tract is a potent factor in the production of deficiency diseases, is indicated by cases of intestinal resection or of sprue. Although frequently indulged in, continued catharsis rarely seems to be responsible, of itself, for obvious manifestations of vitamin B deficiency. The catharsis in our patient was very frequent, chiefly because of the persistance of the nausea, and despite the fact that the symptoms due to vitamin B deficiency were increased, the catharsis was probably a measure of value as regards the intake of other substances in the diet.

SUMMARY

In summary, a case of vitamin B deficiency in association with disease of the gall bladder is herewith presented. The anorexia, epigastric distress, neuritis and dermatitis present during the period of the disease are discussed as regards their clinical significance. The factors responsible for deficient amounts of the several vitamin components in the various tissues are also noted and discussed.

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Mucous Colitis, Complicated by Colonic Polyposis, Relieved by Allergic Management

Report of an Instance

By

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THE allergic nature of mucous colitis and its successful management by specific food elimination has been commented on by Vaughan (1) and Hollander (2). The possibility of hypersensitive reactions on all mucous surfaces has been emphasized by numerous writers. Nasal polyps are quite frequent in allergic hypersensitive rhinitis, and proper treatment by the removal of foods and inhalants tends, not only to cause their disappearance but to prevent their recurrence (3). That colonic polyposis, particularly the pseudo or post inflammatory type (4) might be a condition analagous to nasal polyposis and of an allergic nature is suggested by a case of mucous colitis complicated by colonic polyposis which was symptomatically relieved by food restrictions. That colonic polyposis does, at times, disappear spontaneously, in no way detracts from symptomatic relief in this case as symptoms can be reproduced at will. In the present case, allergic management was undertaken because of a suggestive allergic history, because of the presence of an eczema and a definite mucous colitis and to try allergic management as a last resort in the effort to prevent the necessity of the removal of the colon, as the indications for colectomy were rapidly becoming more urgent.

Mrs. N. M. B., a housewife, aged 35, had as a complaint, soreness in the rectum, obstinate constipation, and generalized abdominal pain and distention. Constipation was not a matter of hard stools but rather a difficulty in passing more than a very small amount of feces at a time. There was an increase in abdominal and rectal pain at each attempted evacuation and there was also considerable blood and mucus passed with each stool. The onset of this illness had been gradual over a period of two years, but had been getting much more severe, and the effort to secure a complete evacuation of the bowels had not only been becoming exhausting but had been consuming from three to four hours each day. At the beginning of the illness there was merely a generalized soreness of the abdomen which had progressed to a cramping pain over the entire lower abdomen with marked exaccerbations of pain before and during bowel movement. There had been a gradually increasing abdominal distention and increasing soreness of the rectum. The bowels had been normal before the onset of the pain. For some months before the onset of abdominal pain, the patient began to notice mucus in the stools which increased in frequency and quantity and for the past year had been accompanied by blood. As difficulty in evacuation increased, enemata were resorted to each day; but with results which became less and less satisfactory and several enemata were taken each day. Enemata were not expelled as a whole but there were always several small passages of water accompanied by a small amount of feces, mucus and blood over a period of several hours. As there was always a sensation of incomplete evacuation and also generalized abdominal pain and distention until the colon was emptied, several enemata were always required to give even partial relief. About six months previous to examination, the patient had been examined elsewhere and had been advised to have an appendectomy. This advice was taken and the patient was told subsequently that the appendix and an ovarian cyst had been removed. All previous symptoms had been greatly exaggerated since the operation. There had been no nausea or vomiting at any time and the appetite had been fairly good. The diet had been unchosen. There had been a loss of about twenty pounds in weight during the period of illness and there had been considerable fatigue which was unusual. The past health had always been good with the exception of a chronic sinusitis for a number of years. There had been much nasal treatment but of late the patient had discontinued treatment as she thought it seemed to aggravate her nasal condition rather than help it. There was a frontal and occipital headache at times and a pain in the back of the neck and in the right arm was usually present when the headaches occurred. The nose was always excessively moist and there had always been an excessive amount of sneezing. An itching skin eruption had been noticed intermittently and there was an itching eczema on the eye lids and about the nose. The patient's parents are living and well and there are two sisters living and well. There was no family history suggestive of allergy. The patient's husband is living and well and her one child is living and well. There have been no miscarriages. The menstruation has always been normal and regular.

Physical examination: Hyposthenic habitus, pale and undernourished. Blood pressure 120/80. There was a moderate amount of acne over the back and chest. The skin about the nose, the eye lids and the eyes was reddened and rough. There was a marked tache cerebrale. The pupils reacted to light and on accomodation. The nostrils were clear but the nasal mucosa was excessively moist. The teeth were in good repair and well kept. The throat was slightly reddened. The thyroid was not palpable. The heart was normal in size and the sounds were clear. The lungs were normal. The abdomen was distended with gas,

Symptoms:

1. Pain
2. Night Pain
3. Nausea
4. Vomiting
5. Gas
6. Bloating
7. Constipation
8. Diarrhea
9. Headache
10. Dizziness
11. Sneezing
12. Nasal Symptoms
13. Cough
14. Asthma
15. Toxemia
16. Hives
17. Eruption
18. Itching
19. Palpitation
20. Dyspnea
21. Joint Pains
22. Bruises

Directions:

Keep your diet as simple as possible. Chart your important symptoms by number in column indicating hour in which they occur. Certain foods are causing your illness, whether it is headache, arthritis, peptic ulcer, asthma or pain. The foods responsible can be determined by a careful diary. Your cooperation is essential for success. List visits to barber shop, beauty parlor, theatre, etc. List anything unusual. Do not take any medicine not prescribed.

Remarks:

X. Symptoms persist.
XX. Symptoms exaggerated.
Z. Symptoms relieved.

These foods are to be omitted:

Date					Date					Date				
Breakfast	1st hr.	2nd hr.	3rd hr.	4th hr.	Breakfast	1st hr.	2nd hr.	3rd hr.	4th hr.	Breakfast	1st hr.	2nd hr.	3rd hr.	4th hr.
Lunch					Lunch					Lunch				
Dinner					Dinner					Dinner				

Form 1—Dietetic "Diary" devised to enable patient to record effects of foods upon symptoms, etc.

and, though there was generalized tenderness throughout, there were no organs palpable. There was a midline post operative scar.

Sigmoidoscopic examination made by Dr. Leith H. Sclocum, who referred the patient was reported as follows: Unable to proceed beyond five and one-half inches. At this level, the lumen of the bowel was apparently narrowed and turned abruptly to the left. The mucous membrane at this point shows what appears to be a polypoid formation. There is no bleeding around the polypoid area. The mucous membrane below this point is fairly normal except that it is congested. The first and second Houston valves appear normal. There are two hypertrophied papillae seen in the anal canal and there is also a slight fissure which is to be seen posteriorly. Report dated September 23, 1934.

A barium enema done at this time showed a very marked and extensive polyposis throughout the colon. This is shown in Figure 1. The urine was entirely negative. The blood picture was that of a moderate degree of secondary anemia.

Protein tests were done by the intracutaneous method and those foods which produced the most pro-



Fig. 1. Barium enema with air injection showing extensive polyposis throughout colon. September 11, 1934.

nounced reactions were eliminated from the diet. The restricted foods were beet, cauliflower, chicken, coffee, corn, pepper, pork, white potato, rice, salmon, sweet potato, and wheat. The restrictions were imposed on September 20, 1934. After a trial of one week there was little or no appreciable change. After another week of the same routine, the only change was that the eruption was a little worse. It was noted that milk had been taken more freely during the two preceeding weeks than had been the usual custom, so milk was added to the proscribed list as an experiment. In the meanwhile a form of diary (Form 1) had been devised for this patient in order to keep a more accurate record of her symptoms during the day after the ingestion of each meal, as it was felt that positive skin tests were of little value as a means of specific diagnosis of allergens. On October 11, 1934, the eruption had about cleared up and the patient reported that the bowels were moving occasionally without recourse to an enema. One week later the skin eruption had disappeared entirely and the patient considered that the bowels were from 50 to 75% better, and though there was mucus in the stools, that the blood had disappeared. From October 22 to October 27, the bowels moved thoroughly and adequatey without an enema. There was abdominal pain and distention on October 27, which was relieved by an enema. It was recorded in the diary that tomato had been eaten on that day for the first time in five days. Tomato was removed from the diet and wheat and rice were added. A later feeding of tomato proved that it was an actual allergen. In the same manner it was found that egg was also a factor and that progress was more apparent after its removal. Milk and egg were replaced in the diet on November 30, 1931, in order to prove them as allergens and as a result, the eruption reappeared, there was an increase in abdominal discomfort and an increase in mucus discharge. During the next few weeks milk, egg, pineapple, banana, and tomato had been proved by clinical trial to be able to increase symptoms, so they were all permanently removed from the diet. From this time on each food of ordinary use was replaced separately in the diet and careful note was made of its effect. White potato and pork were proved to be allergenic and again progress was more apparent after the total elimination of these foods. On February 7, 1935, the patient reported that she felt perfectly well and as though there was nothing at all the matter with her. The bowels were moving each day without difficulty and mucus was appearing in the stools at rare intervals only. It was observed that mucus appeared only if wheat was eaten consistently or if the diet was broken deliberately. Wheat apparently had an accumulative action that could be avoided by including it in the diet no oftener than every fifth day. By February 14, there was no longer any evidence of polypi by sigmoidoscopic examination, and by barium enema there was a definite diminution of the original number of polypi throughout the colon. Sigmoidoscopic examination by Dr. Leith H. Sclocum made February 25, 1935, was reported as follows: Patient again examined, and while I am still unable to get into the sigmoid, the polypoid formation noted in the previous report is not present. The mucous membrane throughout is entirely normal. The anal canal presents the findings noted in the previous report.

Periodic examinations by barium enema have been made and serve as an index to the clinical improvement of this patient as they demonstrate a steady decrease in the number of polypi. Films, taken at vary-



Fig. 2. Barium enema with air injection made February 14, 1935.



Fig. 3. Barium enema with air injection made July 22, 1935.



Fig. 4. Barium enema without air injection made September 8, 1935.

ing intervals, by means of the opaque enema are shown. The patient has regained her lost weight and is perfectly comfortable as long as she remains within her dietary limitations. Restriction of specific foods in this case has had the effect of relieving not only the major complaints but also the two minor ones of eczema and hypersensitive rhinitis. As there has been no effort made to avoid contacts and inhalants it follows that the relief obtained from nasal symptoms was due to restriction of foods that were producing inflammatory reactions in other mucus tissues. The etiological factors in this case of mucous colitis have apparently been removed by the elimination of a few foods, which, when re-introduced into the diet cause a prompt return of abdominal pain associated with the presence of mucus in the stools. Removal of these irritants has been accompanied by the cessation of all symptoms of colitis and by an apparent diminution of colonic polypi. In this instance it seems that the specific treatment of colonic irritation has indirectly been helpful in the eradication of a majority of colonic polypi just as specific treatment of hypersensitive rhinitis tends to promote the disappearance of nasal polypi and to prevent the recurrence of those which have been removed surgically.

A new form of food diary which is self explanatory and which permits an hourly and daily record of symptoms after meals was devised for this patient. The diary is useful in any type of allergy and constitutes an accurate and permanent record of the individual's reaction to a compatible diet, to trial diets and to suspected foods purposely included in the diet.

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Selenium-Toxicosis: the Etiologic or Causative Factor in Pellagra?

By

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SELENIUM *(Se = 79.2)*, and other like non-metallic compounds as tellurium, etc., belong to the sulphur group. Selenium occurs in various blends and minerals, three allotropic forms being known at present. The chief source of the element is iron pyrites in which part of the sulphur content is replaced by selenium, though it may be widely distributed throughout nature associated with sulphur in some form. In the pure state, selenium is steel-grey in color, is a good conductor of electricity when exposed to light but a poor one when in the dark. It is very sensitive to light, possesses the power of fluorescence, which property seems to bear some connection with its ability to photosensitize. In this respect it resembles the iron-free photodynamic substance "hematoporphyrin" which is sometimes found in the body under abnormal conditions, and which may be made synthetically by the action of sulphuric acid on hemoglobin. There appears to be some relationship between selenium and other fluorescent compounds such as "chlorophyll-zeochin" a substance found in corn, and to "flurophile" which is found in the bodies of certain animals dying of the disease "fagopyrism."

According to Gassmann (1), selenium is found in the human body in minute amounts, healthy teeth containing about 0.056%. Selenium is also to be found in the urine, 0.0011% in males, and 0.00009% in females. He offers no explanation why the greater amount is found in male urine.

The physiologic action of selenium and its compounds has been little studied or understood. Selenium itself apparently exerts no poisonous action but the alkali selenites, and selenates, are very poisonous. This toxic effect resembles that of arsenic and fluorite poisonings.

Selenium Oxide (SeO), when given internally in minute amounts, appears to carry oxygen to the body sulphur, combining with it, and does not easily lose its effectiveness as an oxydizing agent. This compound in the system will cause an increased sulphuric acid secretion and for this purpose has been used in the treatment of malignant diseases, as it is known there is a diminution of this acid in those diseases.

Selenium Oxychloride ($SeOCl_2$), another selenium compound, has very peculiar and uncommon solvent properties. It has a selective solvent action on such resistant materials as hair, silk, rubber, enamel, "bakelite," the hydro-carbons, etc. It appears also to have a solvent effect on the outer coverings of the grains (buckwheat, corn, maize, rice, etc.), and perhaps adversely affects the vitamins contained therein.

Selenium compounds are known to destroy the diastasic-like action of saliva (2). They also have been used in the treatment of amebic infections, being known to kill the *endameba hystolytica*. This effect is probably due to the solvent action of the compounds on the outer cellulose-like coat or ectosarc of the ameba, and perhaps also to some photosensitizing affect on the ameba itself which is very light-sensitive.

When animals have eaten plants poisoned by selenium, they become crippled, and die in great numbers especially on being exposed to the bright light of the sun. The disease "blind staggers," and "alkali disease" found among live-stock has definitely been traced to this toxic irritant substance, selenium (3). Animals apparently are able to detect the plants containing lethal doses of the poison and leave them alone, but certain species of leguminous plants and grains, which they do eat may contain dangerous amounts of the toxic substance. Though the amount of the poison taken into the body may be small, the long and continued ingestion would no doubt lead to a toxic accumulation in the body.

So close a relationship exists between selenium and sulphur that plants are unable to distinguish them apart, utilizing the one when the other is absent from the soil. The remedy of this situation, as pointed out by the United States Department of Agriculture, is to add sulphur to the seleniferous soil, that the undiscriminating plants will get a great deal more of it than they do of selenium. The amount of this toxic element diminishes in proportion to the amount of the sulphur added.

A marked resemblance will be noted on comparing the symptoms of selenium-toxicosis in animals to the symptoms of pellagra in man. The most striking of these are:

1. Both suffer severely from gastro-intestinal disturbances, nervous and mental disorders which often terminate in complete dementia.

2. On exposure to the bright light of the sun during the Spring and Summer months, skin manifestations present themselves in the form of vesiculations and actinic dermatites. The other symptoms present become more aggravated, and it is at this time the mortality is at its highest.

3. During the Fall months, the skin commences to desquamate, and by wintertime atrophic and pigmented areas resembling vitiligo make their appearance. (In man, if these pigmented patches make their appearance on the back of the hands and forearms, suspicion of pellagra should be immediately aroused).

4. The pellagrins, in addition to a capricious appetite or anorexia, complain also of a burning sensation of the tongue and throat, and there is often a complaint of a garlic or arsenic-like odor in the mouth and breath. A somewhat similar offensive odor is noted on and about selenium poisoned animals. This odor is probably due to the carbon di-selenide or methyl selenide, and closely resembles the smell of de-

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cayed radishes. It is said carnivorous beasts will not eat the flesh of animals poisoned by selenium on account of the presence of this obnoxious odor.

Another disease among animals (dogs) known as "black-tongue" corresponds closely with the geographic distribution of pellagra. Goldberger was able to produce in dogs an experimental condition similar, if not identical with pellagra, by a type of diet found to be associated with the occurrence of pellagra and which had caused pellagra to be produced in the human (4). He concluded though the factor P-P, now called vitamin G or B_2 was the controlling factor in pellagra, and in "black-tongue."

It is known that certain chronic alcoholics develop typical symptoms of pellagra after imbibing the cheapest of whisky or so-called "corn." If this liquor should be made from grains and plants that have been poisoned by selenium or similar poison, more or less of the toxic substance would find its way into the liquor, setting up a chain of symptoms, especially in those with a lowered tolerance to such a poison, thus accounting for the so-called alcoholic-pellagra syndromes.

Pellagra has generally been ascribed to a lack of sufficient pellagra preventing substances in the diet, but the factors underlying this deprivation are many and various. As early as 1776, Venice passed legislative measures prohibiting the sale or exchange of all ill-smelling, ill-tasting and discolored corn. Even to this day, the hypothesis is that corn and like foodstuffs lack something essential to the proper nutritional rhythm of the body; in other words, they are "deficient" (5). In the South, where there is a large rural population of the poor laboring class, pellagra should be expected, but in Mexico, where the economic and social conditions of the rural people are similar to our potential pellagra population, there is comparatively little pellagra (6).

Why pellagra should become so prevalent, even on the increase, when the knowledge of vitamins and nutrition is now so well understood, remains unexplained. Statistics show today that over 30% of large groups of hospital patients die or go into chronic progressive illness in spite of what appeared to be ample opportunity of vitamin therapy to have been effective (7).

This rather poor showing of vitamin therapy in pellagra would only point to a cause other than one of a nutritional deficiency.

It is known that a diet of animal flesh, liver, salmon, egg-yolk and leguminous vegetables possess curative and preventative powers in pellagra. These foods are all rich in sulphur. As there is a disturbed sulphur metabolism in both pellagra and selenium poisoning, and, as sulphur has an affinity for selenium and *vice versa*, the administration of sulphur and diet rich in sulphur-containing foods would appear to be the proper curative and preventative measures to be instituted for both these disorders.

It is surprising that no extensive searches have been undertaken on the food and soil of pellagrinous districts to determine the presence and concentration of such toxic substances as selenium that might be the etiologic or causative factor of pellagra (8).

CONCLUSIONS

The present state of knowledge concerning the cause of pellagra is still unsatisfactory.

The rather poor showing of vitamin therapy in pellagra would only point to a cause other than one of a nutritional deficiency.

A striking resemblance is to be noted between the symptoms of pellagra and selenium poisoning, and there is reason to believe this disease is the result of a similar poisoning. The toxic poisoning is absorbed from the food in the alimentary tract and spreads throughout the body, concentrating principally in the liver where it does the greatest damage. That it acts perhaps as an oxydative catalyst by causing the destruction of certain vital food constituents by oxydation, or by preventing the proper absorption, assimilation or utilization by the body of the food in an adequate manner may be possible.

The actinic dermatitis present in these cases, and excited by exposure to sunlight could be due to the fluorescent substance, hematoporphyrin, or some similar-acting photodynamic substance in the bloodstream which is capable of sensitizing the skin to sunlight. This substance is apparently manufactured in the body as the result of the action of the toxic substance (selenium?) on the body sulphur whereby the resultant increased sulphuric acid of the body acts on the hemoglobin forming the photo-sensitizing substance.

As there is a disturbed sulphur metabolism in pellagra, a diet that is rich in sulphur, and the institution of sulphur therapy, would appear to maintain immunity against the disease. If, on the other hand, the body tissues should be so extensively damaged and beyond Nature's repair, then any food, vitamin, or for that matter, any therapeutic measures would be unlikely to restore structures so injured and would be of no avail.

Chemical examinations and spectroscopic analyses should be made of the foods and soils in pellagrinous districts to determine the presence, and concentration, of any and all toxic substances, that the proper study of toxic limits, tolerance limits, diagnostic symptoms, and remedial measures could be undertaken thus safeguarding the public health within the areas affected.

ADDENDUM: Even if the basis of this new theory should prove incorrect, and fall by the wayside along with the many other theories thus far advanced—nevertheless it should only spur one on to greater intensive research in solving the problem, the cause and the cure of pellagra.

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SECTION V—*Therapeutics*

II. Effect of Prolonged Administration of Salicylate Upon Nitrogen Metabolism and Plasma Carbon Dioxide Combining Power in the Dog*

By

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A REVIEW of the literature indicates that the administration of salicylates increases nitrogen metabolism (1-8). Some observers report a subsequent compensatory decrease during the post-administration periods (9-11). However, Jolin (12) reports that salicylates have no influence and Wiley (13), Morris and Graham (14) report that salicylates exert a slight inhibitory effect on nitrogen metabolism. Our work was done in an endeavor to clarify the literature on this point, and to determine if calcium gluconate in any way influences the effect of acetylsalicylic acid on nitrogenous metabolism. At the same time we studied the effects of acetylsalicylic acid and a mixture of acetylsalicylic acid and calcium gluconate on the carbon-dioxide combining power of the plasma which several observers (15-18) have reported to be lowered by the drug. Calcium gluconate was chosen because of its basic ash and because it ameliorates the gastric irritation caused by acetylsalicylic acid (19), without significantly depressing gastric secretion (20).

METHODS

Two groups of normal female dogs were employed. After ten days on a standard diet, seven daily control determinations were made on 24 hour samples of urine and upon the CO_2 combining power of the blood plasma. Residual urine was obtained by catheterization.

The first group of four dogs then received 0.15 Gm. of Merck's U. S. P. acetylsalicylic acid per kilogram body weight *twice* a day for two months. The second group of three dogs received a similar amount of acetylsalicylic acid with 0.07 Gm. per kilo of calcium gluconate twice a day for the same period. When vomiting occurred the drug was given only *once* a day, and the metabolic results under such conditions were discarded. During the period of medication, determinations on the blood and 24 hour urine were made three or four times a week.

RESULTS

Group I. Prolonged daily administration of acetylsalicylic acid resulted in alterations of nitrogen metabolism, as determined by urinary analysis, and of the carbon dioxide combining power of the blood plasma.

The dogs of Group I on acetylsalicylic acid alone developed nausea and vomited on about the third day of medication. To prevent vomiting the dosage was decreased by one-half for one or two days after which the full dose was resumed. Anorexia prevailed for some time but did not prevent the dogs from completely eating their standard meal. The results of analysis were discarded on days when the animals vomited. In this group there resulted first a decrease in total nitrogen output of 11% below normal (dog 1, 17.4% decrease) for the first 20 days and of 6.2% below normal for the second period of 25 days, which was followed by an increase of 15.2% above normal during the third period of 14 days. Urea elimination followed a parallel course; there was a progressive decrease in the total urea output; first period, —10.7%; second period, —24.9%; and then a rise to +117% during the third period. It was found that the ammonia output also decreased 16.4% below normal during the first period and rose to 4.9% above normal in the second period. If the data are not divided into such periods, the average output for the entire treatment period is the same as the control period; that is, the increase during the last two weeks of medication was adequate to annul the decrease observed during the first six weeks.

These dogs showed a definite tendency toward acidosis. The average plasma—CO_2—combining power of dog one was 44.5 vol. per cent; on acetylsalicylic acid medication, it fell during the first period to 37.9, during the second period to 39.4 and then returned to 44.5 during the third period. The pH of the urine showed parallel changes, becoming lowest during the first period of medication and then gradually rising above normal in the third period. The average volume of urine as well as the total output of urinary chloride was decreased under medication with acetylsalicylic acid.

Group II. The administration of calcium gluconate with acetylsalicylic acid to the dogs of group two

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GROUP I

Acetylsalicylic Acid

Date	Dog	Blood Plasma CO_2 Comb. Power Vol. 0/0	Urine (24 hr.) Vol. (c.c.)	S. G.	pH	Total N_2 in (Gms.)	Total Urea in (Gms.)	Total NH_3 in (Gms.)	NH_3 Coef.	Total Cl
Control Period (10/24—11/7)	1	44.5	538	1.021	7.22	7.034	2.314	0.448	0.063	
	2	47.7	595	1.019	8.95	5.322	1.904	3.157	0.593	3.54
	3	46.6	311	1.032	8.37	5.676	2.953	1.291	0.227	3.27
	4	45.3	420	1.022	8.98	5.479	1.778	3.224	0.588	3.22
	Av.	46.0	466	1.023	8.38	5.877	2.237	2.030	0.345	3.34
Drug Period I (11/7—11/28)	1	37.9	554	1.018	6.42	5.811	3.141	0.330	0.056	
	2	46.0	560	1.023	8.70	5.863	1.634	2.240	0.382	3.58
	3	46.3	244	1.039	7.84	4.161	1.960	1.188	0.285	2.58
	4	46.0	477	1.029	8.91	5.119	1.252	3.027	0.591	3.59
	Av.	44.0	458	1.027	7.96	5.238	1.996	1.696	0.323	3.25
	% Change	—4.3	—1.7	+0.3	—5.0	—11.0	—10.7	—16.4	—6.3	—2.6
Drug Period II (12/1—12/26)	1	39.4	437	1.021	7.62	6.294	4.120	1.099	0.166	
	2	51.1	553	1.023	8.81	5.205	1.113	2.810	0.539	3.74
	3	48.6	191	1.027	8.29	4.671	0.648	1.162	0.248	1.50
	4	48.1	669	1.020	8.88	5.882	0.835	3.451	0.586	3.31
	Av.	46.8	412	1.022	8.40	5.513	1.679	2.130	0.386	2.85
	% Change	+1.7	—11.6		+0.2	—6.2%	—24.9	+4.9	+11.8	—14.6
Drug Period III (12/26—1/10)	1	44.5	493	1.022	8.78	8.286	5.023	2.020	0.243	
	% Change	0.0	—8.3	—0.08	+17.7	+15.2	+117.0	+350.9	—29.5	

allay some of the effects produced by the administration of acetylsalicylic acid alone. Nausea and vomiting were delayed or occurred on about the sixth day of medication, and the anorexia was less in degree. Nitrogen metabolism was stabilized; during the first period (first 20 days) of medication the average total nitrogen output was decreased only 2.8 % below normal, while during the second period it rose to 7.8% above normal, and during the third period it was 5.1% below normal. The ammonia and urea output likewise did not show marked variations from normal.

No tendency toward acidosis was evidenced by the determination of the plasma—CO_2—combining power; the latter instead rose from 44.0 to 47.0 during the first period, and then fell to 44.2 and 43.5 during the second and third periods respectively. Associated with this the urine remained alkaline.

The average volume output of urine and the total output of chloride was slightly increased during medication with acetylsalicylic acid and calcium gluconate.

DISCUSSION

Undoubtedly an important factor concerned in the early decrease in urinary nitrogen elimination is the digestive disturbance caused by acetylsalicylic acid. After the first few days the animals became more tolerant to the drug, as evidenced by the absence of vomiting, and later the disappearance of anorexia. After about thirty days the nitrogen elimination returned to normal and then after about forty-five days it was above normal. This phasic reaction may be explained adequately by the early more acute disturbance of digestion causing a decreased nitrogen absorption with a slow return to normal which was then followed by a compensatory increase in the urinary nitrogen as a consequence of the true action of the drug on nitrogenous metabolism. As stated above, this phasic or periodic reaction of nitrogenous elimination would have been overlooked had the data on nitrogenous elimination during acetylsalicylic acid administration been averaged and compared with that of the control period. The foregoing interpretation is supported by the fact that the administration of calcium gluconate definitely decreased the objective digestive symptoms. After the slight digestive disturbances had disappeared, the effect of the acetylsalicylic acid was to augment nitrogenous elimination in the urine slightly but definitely, which would appear to be the true effect of the drug on nitrogenous metabolism.

The administration of acetylsalicylic acid in the doses employed caused a slight but definite "acidosis" during the periods that the digestive disturbances were present, it being more evident during the period of more marked disturbance. Correlated with the decreased plasma—CO_2—combining power, the urine became acid and there was a decreased ammonia coefficient. The acidosis is best ascribed partly to the acid properties of the acetylsalicylic acid and partly to its early toxic action upon the liver and kidney inhibiting normal deamination with an accumulation of amino acids in the blood. The calcium gluconate prevented the "acidosis" partly because of its basic ash and partly because it prevented disturbances of digestive function and deamination of amino acids. As the animals developed a "tolerance" to the dose of acetylsalicylic acid used, there was more complete absorption of nitrogen in the food so that nitrogenous elimination in the urine increased while more complete

GROUP II

Acetylsalicylic Acid + Calcium Gluconate

Date	Dog	Blood Plasma CO_2 Comb. Power Vol. 0/0	Urine (24 hr.) Vol. (c.c.)	S. G.	pH	Total N_2 in (Gms.)	Total Urea in (Gms.)	Total NH_3 in (Gms.)	NH_3 Coef.	Total Cl
Control Period (10/24—11/7)	1	40.7	467	1.023	8.70	5.941	1.641	1.130	0.190	
	2	45.0	353	1.029	8.60	6.291	2.537	1.527	0.242	3.46
	3	46.5	331	1.031	8.82	5.436	2.247	2.461	0.452	3.35
	Av.	44.0	350	1.027	8.70	5.889	2.145	1.706	0.289	3.40
Drug Period I (11/7—11/28)	1	44.6	483	1.021	8.43	5.769	2.982	1.180	0.208	
	2	45.8	385	1.029	7.76	5.668	2.390	1.628	0.287	3.31
	3	50.6	360	1.033	8.50	5.749	1.851	1.930	0.335	3.36
	Av.	47.0	407	1.027	8.23	5.725	2.407	1.579	0.275	3.48
	% Change	+6.8	+16.2	0.0	—5.4	—2.8	+12.2	—7.4	—4.8	+2.3
Drug Period II (12/1—12/26)	1	39.2	447	1.025	8.96	6.343	3.224	2.318	0.365	
	2	44.5	523	1.026	8.78	6.868	1.136	2.851	0.415	3.36
	3	49.1	456	1.026	8.70	5.829	1.302	2.767	0.474	3.56
	Av.	44.2	475	1.025	8.81	6.346	1.887	2.645	0.416	3.46
	% Change	+0.4	+35.7	—0.1	+1.2	+7.8	—12.0	+55.0	+43.9	+1.7
Drug Period III (12/26—1/10)	1	43.5	482	1.022	9.04	5.635	2.661	2.234	0.396	
	% Change +6.8		+3.2	—0.1	44.9	—5.1	+62.1	+97.6	+108.4	

deamination was adequate to compensate for the "acidosis."

The foregoing interpretation of the evidence, we believe, is the most simple and direct view of the effect of calcium and is preferable to the alternative hypothesis that the calcium in some way improved in the early periods tissue metabolism of nitrogen. This leads us to the view that the true effect of acetylsalicylic acid on nitrogenous metabolism of the body tissues is to increase it. Thus, we maintain that the results of those who have reported a decrease in nitrogen metabolism on salicylate administration, are due chiefly to digestive disturbances leading to a decrease in the absorption of nitrogenous food stuffs from the intestine.

It is pertinent to point out that Mutch (21) has reported that mildly toxic doses of calcium-acetylsalicylate given with traces of calcium chloride interfere less with the ossification of cartilage and the growth of young rats than do equivalent amounts of acetylsalicylic acid itself.

SUMMARY AND CONCLUSIONS

1. Prolonged daily administration of acetylsalicylic acid (0.15 Gm. per kilo twice a day) resulted in digestive disturbances, alterations of nitrogen metabolism and a tendency toward acidosis in dogs. The average total nitrogen output on continued medication was decreased 11% below normal during the first twenty days, 6.2% below normal during the following twenty-five days and was increased to 15.2% above normal during the following fourteen days. "Acidosis" was evidenced during the first two periods by a decreased plasma-carbon-dioxide-combining power, an acid urine and a decreased ammonia coefficient.

2. The administration of calcium gluconate (0.07 Gm. per kilo twice daily) with the acetylsalicylic acid ameliorated the untoward effects of acetylsalicylic acid. Nitrogen metabolism was stabilized as evidenced by a more uniform output of urinary nitrogen. Early acidosis was prevented; the plasma carbon-dioxide combining power increased slightly, the urine remained alkaline while the ammonia coefficient was not decreased to such a degree as it was with acetylsalicylic acid alone.

3. It is concluded that the decreased nitrogenous metabolism reported by some observers is due chiefly to digestive disturbances and the true effect of acetylsalicylic acid on nitrogen metabolism is to augment it slightly when large doses are administered.

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Glutamic Acid Hydrochloride as a Substitute for Dilute Hydrochloric Acid in Achlorhydria*

By

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All investigators who have studied the problem of artificially administering hydrochloric acid agree upon one point, i.e., that it is impossible to duplicate the continuous secretion in the stomach by substitution therapy [6, 8, 16]. However, the indications for the use of this acid are numerous and seem to be increasing as indicated by frequent reports of its beneficial effects. The symptoms of "dyspepsia" have been given as indications for the use of HCl [14], [15], [17]. Hydrochloric acid has been recommended in chronic cholecystitis [1], asthma [3], [7], prophylactically in the curative course of the stomach [12], pernicious anemia [5], sciatic disease [20], eczema [21], typhus [22], and acne vulgaris [4]. While there is a decided amount of abnormal acid in the stomach contents

The use of HCl is not without its dangers to the teeth [23] unless it is well diluted and an alkaline mouth wash is used afterward to neutralize it. For this reason, preparations have been sought which would deliver acid to the stomach yet could be taken in tablet or capsule form. Glutamic acid hydrochloride is one of these preparations.

Glutamic acid has been found to have antiacetonuric effects [2], [9] when used in conjunction with iron. However, other authors [10], [18] were unable to substantiate the hemopoietic stimulating effect. Tarozzi [21] and Mellon [19] considered that glutamic hydrochloride does not stimulate to the secretion of HCl. However, since no report could be found in the literature showing the concentration of acid produced in the stomach by this preparation, the present study was undertaken to determine the effectiveness of glutamic acid-HCl in liberating free HCl in the stomach. It can be administered easily, and if it proves to be as effective as dilute hydrochloric acid then the disagreeable taste and danger of dilute acid can be avoided.

METHOD

A group of 19 patients with achlorhydria were selected from the Medical Clinic of Northwestern University. The group contained 8 patients with pernicious anemia, and 7 of the entire group were men. The ages of the patients averaged 60 years. In most instances a histamine gastric analysis had been performed, but this was repeated to insure that these patients did not secrete HCl. One-tenth milligram of histamine hydrochloride was injected subcutaneously for each 10 kilograms of body weight. Besides the fasting contents, the total amount of secretion was withdrawn every 20 minutes for 80 minutes. In no case was acid found. Titrations for free and total acid were performed in the usual manner and the pH was determined by the quinhydrone electrode.

In order to study the effectiveness of the glutamic acid, the patients returned to the clinic about once a week and the fasting contents of the stomach were removed. Glutamic acid hydrochloride capsules were given with 200 c.c. of tap water, since tap water was found on numerous occasions to have a pH more nearly 7.00 than did any available distilled water. Specimens

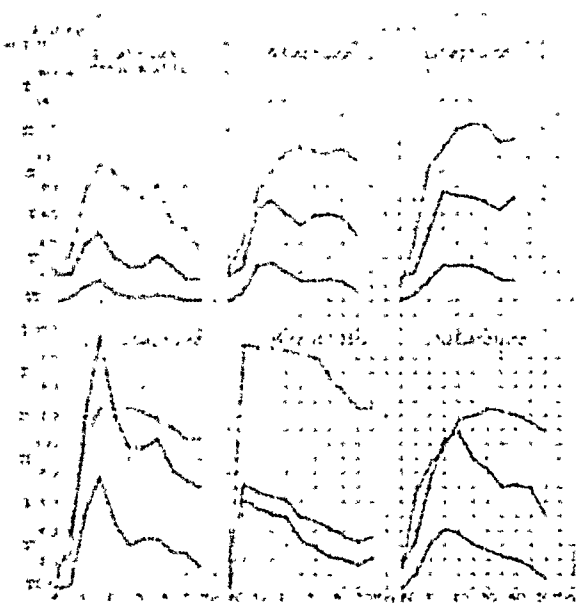


Fig. 1. Average free and total acid (solid lines) and pH curve (broken line) on 17 to 19 patients with achlorhydria. 200 c.c. water used with each test.

of 6.0 c.c. were removed every 5 minutes until the stomach was empty. In but few instances was it possible to get specimens after 50 minutes, which meant that 60 c.c. of the original 200 c.c. had been removed through the tube and the remainder presumably had gone through the pylorus. Five c.c. were used to determine the pH, and 1.0 c.c. was necessary for the titration of free and total acid. The titrations were carried out with N/30 sodium hydroxide because of the small amount of material, and the data then recalculated to the usual "clinical units."

The patients were given 1 capsule of glutamic acid-HCl on one day, 2 capsules on the next visit, and so on

up to 10 capsules. Only one test was performed on one day. In one test, 4.0 c.c. of dilute HCl (U.S.P.) were injected through the tube with 200 c.c. of water. Specimens were withdrawn similarly. This is the usually recommended dose of HCl.

The amount of glutamic acid in each capsule is 0.28 grams, which should deliver 8.45 minims of acid equivalent to the usual 10 per cent hydrochloric acid. Therefore, 7 capsules should equal the dilute HCl in one teaspoonful.

RESULTS

The results of the determinations were averaged and the curves derived are shown in Figure 1. Each line shown does not represent the average of the same number of analyses because of the difficulty encountered in having patients return for the tests. However, in no instance were data on less than 12 patients used; the largest number was 19.

Figure 1 shows the average effect of 2, 4, 6, 8 and 10 glutamic acid hydrochloride capsules and the results when 4.0 c.c. of dilute hydrochloric acid were used. The alternate curves representing the results with 1, 3, 5, 7 and 9 capsules are available but are not included here, since they are no more informative than those presented. Throughout Figure 1 the average free and total acid curves are represented by solid lines and the pH by broken lines. In general, as might be expected, the acid values increased when larger numbers of capsules were administered. Eight capsules produce on the average the greatest concentration of free and total acid in the stomach. which was higher than when 4.0 c.c. of dilute HCl were used. When 10 capsules were given the acid values were lower than after 8 capsules; this must be ascribed to variation within the limits of accuracy of the procedure, since these two curves are averages of results on the same group of patients. Such variations are commonly present when gastric analysis figures are compared.

The results suggest that 8 capsules of glutamic acid-HCl produce the highest free and total acid for the 200 c.c. dilution used. However, it should be remembered that the total difference in acid administered on any two alternate tests was equivalent to only 17 minims of HCl.

When 6, 8 or 10 capsules were administered, the average pH reached approximately 3.0 and was maintained there for the 50 minutes that the material was in the stomach. The curve reached its height at the end of 10 minutes. A pH of 1.0 was attained when the dilute HCl was given. This level may be inferred to have been reached immediately, and the acid emptied slowly from the stomach. From a bactericidal standpoint (13) this level (pH 1.0 to 2.0) would be desirable, but it should be remembered that these figures merely represent the acid present in a dilution of water and stomach secretion. This amount would be quickly neutralized if only a small quantity of food were consumed.

COMMENT

When individual patients are considered, there are wide divergences in the acid values developed following the administration of these capsules. Thus, arbitrarily selecting the results when 8 capsules were used and considering the specimens obtained 10 minutes after the ingestion of the capsules, one patient showed: pH 1.70, free acid 230, and total acid 400. Another patient showed: pH 7.03, free acid 0, and total acid 15 for this same 10 minute period. The latter patient attained his greatest concentration of acid at the end of 20 minutes: pH 2.10, free acid 65, and total acid 173. Throughout the entire study similar wide variations were noted. Variations also occurred following the administration of dilute HCl but were not so extensive. The maximum acid values attained by individual patients receiving 8 capsules were observed on the tenth to the fortieth minute period.

A free acid reading of 230 seems high and might be thought to be dangerous to the lining of the stomach. However, Mahler (19) studied the effects of this preparation and observed the action on the gastric mucosa through a gastroscope. He could find no ill effects.

It would seem that the capsules may not have disintegrated so quickly in some patients as in others. When the capsules were put into warm water and the containing vessel slowly rotated, it was noted that 2 or 3 minutes were necessary for the capsule to break up and 5 or 6 minutes elapsed before most of the glutamic acid-HCl went into solution. However, all the material did not leave the capsule. By inference, it may be assumed that some of the hydrochloride may have passed undissolved into the intestines.

Another reason for the differences in individual readings was due to the failure of mixing the acid with the water and the stomach contents. Perhaps this difficulty might have been overcome by withdrawing all the contents at each 5 minute interval and replacing all but the 6.0 c.c. necessary for the determinations. This was not done, and would not be done if patients were given these capsules for therapeutic purposes to take in place of the fluid hydrochloric acid. At best, an imperfect mixing of acid must result when capsules are ingested.

The question of the advisability of using HCl in therapy will not be discussed. The indications, both past and present, are numerous. It must also be appreciated that substituting hydrochloric acid in amounts equivalent for the normally present acid is still impossible. However, it must occur to everyone that there are advantages in the use of capsules when acid is to be prescribed. Concentrations of acid can be developed with the use of these capsules equal to and greater than can be found with the usually recommended dose of 4.0 c.c. of HCl. The convenience of this method has much to commend it. It is easier to swallow several capsules than to sip acid through a straw, particularly when the many cautions given the patient with the prescription for fluid acid make him fearful.

When the capsules were given to patients with hypochlorhydria, no great stimulation of acid was found. This is contrary to the findings of Tagawa (24) and Mahler (19).

A prolonged clinical trial to test the possible beneficial effects of the glutamic acid hydrochloride was not done. However, from the present results it would seem that for a dilution of 200 c.c. 8 or 9 capsules should be used.

SUMMARY

This study of 19 patients with achlorhydria permits the observation that using 8 or 9 glutamic acid hydrochloride capsules (0.28 gm.) with a glass of water (200 c.c.) produces free, total, and pH readings that

compare favorably with the results of 4.0 c.c. of dilute hydrochloric acid.

Note: Miss Florence Burdahl gave expert technical assistance.

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Phenolphthalein Studies*

III. Phenolphthalein and Activated Charcoal

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THE wisdom of the introduction, in the 11th edition of the United States Pharmacopoeia, of Activated Charcoal instead of mere charcoal and of making efficiency rather than source the criterion for its official standing, is well illustrated by the relation of phenolphthalein to charcoal: for charcoal that would have been acceptable in accordance with the U. S. P. X requirements may be entirely worthless as an adsorbent of phenolphthalein, while activated charcoal, U. S. P. XI, is an active adsorbent of phenolphthalein.

The idea having been expressed that charcoal is a useful remedy in cases of phenolphthalein overdose, experiments were undertaken with several kinds of charcoal we had on hand in the laboratory and that would have satisfied the requirements of the Xth edition of the U. S. P. with the following results (Table I, Part A).

It will be seen that none of these varieties is likely to have much antidotal value in phenolphthalein overdose, as they merely adsorb from 0.1 to 1+% and it will also be seen that none meet the requirements for activated charcoal U. S. P. XI: these being as follows:

"Dissolve 0.25 Gm. of methylthionine chloride in enough distilled water to make 250 c.c. of solution. Measure exactly 50 c.c. of this solution, at 25° C., into each of two 100-c.c., glass-stoppered flasks. Add to one flask exactly 0.25 Gm. of activated charcoal, stopper the flask, and shake it vigorously for five minutes. Filter the contents of each flask through a filter, which has not been previously moistened, rejecting the first 20 c.c. of each filtrate. Measure exactly 25 c.c. of the remaining filtrates into each of two 250-c.c., volumetric flasks. Add to each flask 50 c.c. of an aqueous solution of sodium acetate (1 in 10) and mix thoroughly, then add from a burette 35 c.c. of tenth-normal iodine, keeping the mixture in constant rotation. Stopper the flasks and allow them to stand for fifty minutes, shaking them vigorously at intervals of ten minutes. Dilute each mixture to exactly 250 c.c. with distilled water,

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mix thoroughly, allow to stand for ten minutes, and filter each through a filter, which has not been previously moistened, rejecting the first 30 c.c. of each filtrate. Determine the excess of iodine in 100 c.c. of each filtrate by titration with tenth-normal sodium thiosulfate. Calculate the number of cubic centimeters of tenth-normal iodine consumed in each titration: the difference between the two titrations, multiplied by 5, amounts to not less than 3.5 c.c. (adsorptive power)."

TABLE I

PART A.	U.S.P. XI Assay c.c. N/10 Iodine	Percentage adsorbed in relation to weight of charcoal	
		Meth. Blue	Phthn.
A. Wood Charcoal, Mc.	0.286	0.61%	0.12%
B. Bone Charcoal, B.	0.75	1.60	0.31
C. Stick Wood Charcoal	0.85	1.81	0.44
D. Animal Charcoal	0.858	1.83	0.46
E. Wood Charcoal, Va.	0.95	2.02	0.48
F. Animal Charcoal, B.	1.1	2.34	0.57
G. Blood Charcoal, S.	1.66	3.54	0.9
H. Certified Activated Charcoal, Bu.	1.71	3.64	0.99
I. Activated Charcoal, H.	2.2	4.69	1.22
PART B.			
J. Activated Charcoal, Ma.	5.7	12.15%	3.26%
K. Activated Charcoal, E.	5.8	12.36	3.36
L. Activated Charcoal, P.	5.95	12.64	3.56
M. Activated Charcoal, M.	6.27	13.36	3.6
N. Activated Charcoal, M.	6.84	14.57	3.98

It will be seen from Table I, Part B, that the charcoals that meet the U. S. P. XI requirements also display activity in the adsorption of phenolphthalein and that the adsorption of phenolphthalein is proportionate to the degree of methylene blue adsorption, as is well shown by Graph I. This fact has been expressed by Freundlich's rule, which postulates that "different varieties of charcoal show the same order of adsorbing power for different substances" (1).

It is also evident from Graph I that charcoal is approximately four times a better adsorbent for methylene blue than it is for phenolphthalein under the conditions of the experiment: for it will be noted that the percentage adsorbed from 40 mg. of methylene by 0.25 Gm. of charcoal is practically the same as that adsorbed from the same quantity of phenolphthalein by 1.0 Gm. of charcoal.

In the interpretation of the Table as well as of the graph, three factors must be brought out that would alter the results: (1) the hydrogen-ion concentration, (2) the length of time of exposure to charcoal, and (3) the temperature.

HYDROGEN-ION CONCENTRATION

The influence of hydrogen-ion concentration on the adsorption of phenolphthalein is of considerable practical interest, inasmuch as the adsorptive activity of the charcoal when employed to nullify the effect of overdose would be carried on at the pH of the alimentary tract.

To determine what quantity of charcoal is likely to be required to adsorb almost 100% of 0.010 Gm. of phenolphthalein in 100 c.c. of buffer solution, observations were carried on at a pH of 9.0 with different amounts of charcoal. Results are shown on Graph 2. From it, one notes that it requires 0.060 Gm. of charcoal to adsorb almost 100% of 0.010 Gm. of phenolphthalein from its solution at this hydrogen-ion concentration.

When we compare the amount of activated charcoal of best quality (N) required for almost complete adsorption at varying hydrogen-ion concentrations, we arrive at results shown in figures in Table II and graphically in Graph 3.

TABLE II

Showing Amount of Activated Charcoal (N) Required for Almost Complete Adsorption of 0.010 Gm. of Phenolphthalein in 100 c.c. of Buffer Solution (2)

At pH 8.0, amount of charcoal required	0.050 Gm.
At pH 9.0, amount of charcoal required	0.060 Gm.
At pH 10.0, amount of charcoal required	0.080 Gm.
At pH 11.0, amount of charcoal required	0.120 Gm.
At pH 12.0, amount of charcoal required	0.200 Gm.

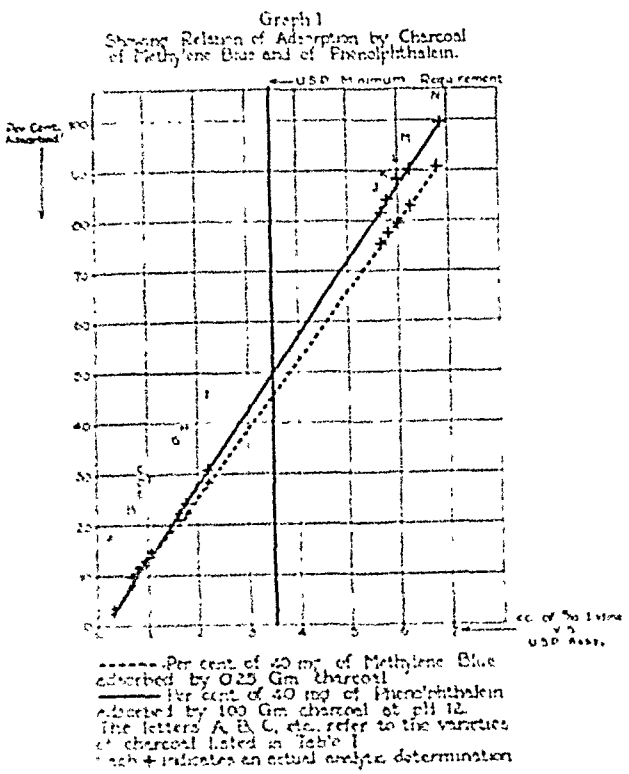
It will be seen from Table II and Graph 3 that the amount of charcoal required to adsorb a given quantity of phenolphthalein is much less at pH 8.0 (which might be considered a point near the alkalinity of the bowel) than it is at pH 12.0. In other words, the adsorptive activity is actually four times greater at the intestinal pH than it at pH of 12.0 that we used in the determinations shown in Table I because it was more convenient for our work. Thus *5 gms. of activated charcoal (N) might be considered a complete adsorbent for 1 gm. of phenolphthalein,* if the time of exposure is 5 minutes and the temperature 25° C. at the pH of 8.0.

Our findings agree in principle with the data of Hauge and Willaman (3) who found that "increasing acidity permits greater adsorption of caramel and of benzoazurin (negatively charged colloids)." These observers also state that alkalinity favors adsorption of electropositive substances, such as methylene blue: while adsorption of non-electrolyte substances is unaffected by the pH ion concentration.

TIME AND TEMPERATURE

It is self evident that variations in time and temperature will alter the results as far as adsorption by charcoal is concerned. Inasmuch as in the system we are interested in, the gastrointestinal tract, a higher temperature and longer time of exposure prevail than those we employed in our test-tube experiments, determinations were made to find to what degree the adsorption of phenolphthalein was changed by increase in time and temperature.

It will be seen from Graph 4 that increase in time of exposure progressively increases the percentage ad-



Graph I

sorbed, so that after sixty minutes there is a 30% greater adsorption than at the five-minute exposure.

Increase in temperature also increases the percentage adsorbed and it does so by about 20% at any length of time exposure.

DISCUSSION OF TEST TUBE EXPERIMENTS

We have found that it required 5 gms. of the best *quality of activated charcoal* (N) to absorb 1 gm. of phenolphthalein at 5 minutes exposure and the temperature at 25° C. As will be noted from Graph 1, the various charcoals that meet the U. S. P. requirements cluster fairly closely together, with the least active being about 20% below the most active. Inasmuch as time and temperature both increase the adsorptive capacity of charcoal by 30% and 20% respectively, we may consider these influences to be adequate to neutralize differences in adsorptive power of various official activated charcoals.

PHENOLPHTHALEIN WITH CHARCOAL IN THE CAT

We have found that, when cats are fed 2% or 4% of phenolphthalein in their daily food ("Kitty Ration" and skimmed milk), it generally is without cathartic action; but that 8% of phenolphthalein in the cat's food usually has a laxative effect. This latter dose is somewhat less than 3 gms. per kg. of the cat's body weight.

By increasing the dose of phenolphthalein to 3 gms. per kg. and giving this by stomach tube, just before the day's food was offered, we secured laxative action in 7 out of 8 instances, as shown by Table III, Part A. The probable explanation for the lack of action, on March 24, in cat No. 13, may be found in the fact that, for some reason or other, the phenolphthalein had formed a hard lump, which was attached to but separate from the stool. This cat No. 13 had a definite laxative effect from the same dose on March 17, a week earlier. Taking the results as they stand, we can report that this dose was laxative in 84% of the observed cases, although the probabilities are that, had the lump formation been prevented, we would have obtained a 100% result.

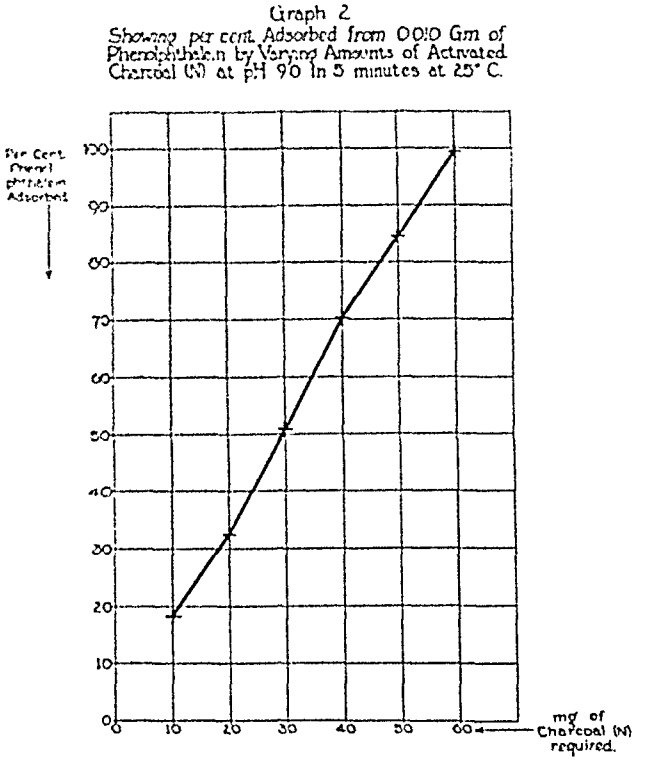
By giving this practically certain cathartic dose of 3 gms. of phenolphthalein per kg. of the cat's body weight mixed with 15 gms. per kg. of Activated Charcoal, we secured results tabulated in Part B of Table III. It will be seen, from this tabulation, that there was no laxative action excepting in one case (Cat No. 2) on March 17; and that, in this cat, the laxative effect was much delayed. A week later, March 24, Cat No. 2 had no laxative effect from the same combination. Summarizing the results as they stand, we may conclude that the charcoal inhibited the laxative effect in at least 84% of the cases.

It is obvious therefore, from this study, that activated charcoal does prevent or much delay the laxative action of phenolphthalein in these cat experiments.

To determine whether the adsorptive activity of charcoal was used up by its passage through the alimentary tract, stool specimens from these cats were studied for their ability to adsorb phenolphthalein. Adsorptive activity was found in only one stool which was passed five hours after the taking of the phenolphthalein. All other stools were obtained 24 or more hours after taking the charcoal and these no longer had any adsorptive power.

PHENOLPHTHALEIN AND CHARCOAL IN THE HUMAN

To determine whether these findings apply to the human, one of us took, on March 17, a dose of 0.30 Gm.



Graph II

TABLE III

Part A. Phenolphthalein Controls

Dose: 3 Gms. phenolphthalein per Kg. of body weight, administered by stomach tube

Date	No.	Wt. Kg.	Gm. Phtn.	Lost	Stools	Action
3/17	5	3.20	9.60	40%	3/17—0, 3/18—Liquid 3/19—Liquid 3/20—Soft	Laxative
3/17	13	2.95	8.85	0	3/18—Formed, Liquid 3/19—Liquid 3/20—Soft	Laxative
3/17	14	2.84	8.52	15%	3/18—Liquid 3/19—Liquid 3/20—Soft	Laxative
3/24	5	3.20	9.60	0	3/24—0 3/25—Liquid 3/26—0 3/27—Liquid	Laxative
3/24	10	2.40	7.20	0	3/24—0 3/25—Semi-formed, Liquid 3/26—Liquid 3/27—0	Laxative
3/24	11	3.10	9.30	10%	3/24—0 3/25—0, 3/26—0 3/27—Liquid	Laxative Delayed
3/24	13	2.95	8.85	0	3/24—0, 3/25—0 3/26—0, 3/27—Formed	None
3/24	14	2.84	8.52	0	3/24—0 3/25—Liquid 3/26—0, 3/27—Formed	Laxative

Part B. Phenolphthalein + Activated Charcoal

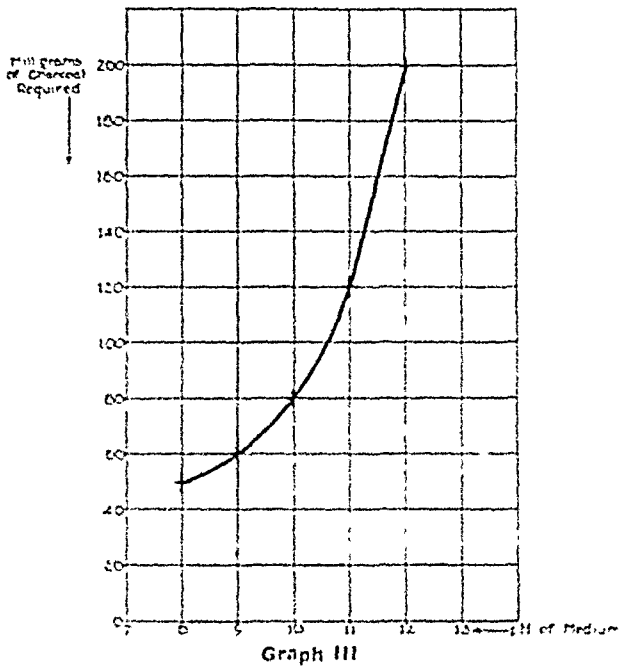
Dose: 3 Gms. phenolphthalein per Kg. of body weight with 15 Gms. activated charcoal (N) per Kg. of body weight, administered by stomach tube

Date	No.	Wt. Kg.	Gm. Phtn.	Gm. Char.	Lost	Stools	Action
3/17	1	3.3	9.9	49.5	25%	3/17—0, 3/18—Formed 3/19—0, 3/20—Formed	None
3/17	2	3.5	10.5	52.5	0	3/17—Two formed 3/18—Two formed 3/19—Formed 3/20—Liquid	Much delayed
3/17	3	2.84	8.52	42.6	0	3/17—Two formed 3/18—0, 3/19—0 3/20—Solid	None
3/24	2	3.5	10.5	52.5	0	3/24—Formed 3/25—Two formed 3/26—Formed	None
3/24	3	2.84	8.52	42.6	0	3/24—Formed 3/25—Formed 3/26—Formed 3/27—Formed	None
3/24	6	3.4	10.2	51.0	0	3/24—0, 3/25—Formed 3/26—Formed 3/27—Formed	None
3/24	12	3.1	9.3	46.5	0	3/24—0, 3/25—0 3/26—Formed 3/27—Formed	None
3/24	C	3.4	10.2	51.0	5%	3/24—0 3/25—Formed 3/26—Formed 3/27—Formed	None

of phenolphthalein in capsule and followed this immediately by five times this quantity (1.5 Gm.) of charcoal (M). This combined dose produced a definite laxative effect lasting two days. Even so, as a dose of 0.12 Gm. always has a more powerful action than was secured from the larger dose with charcoal, the impression cannot be dismissed that a certain degree of inhibitory action was secured. It seems, however, that the 1 to 5 relation of the phenolphthalein to charcoal does not apply to the human. This probably is due to the fact that the total quantity of charcoal taken by the human is very much smaller than that taken by the cat and that most of the enormous dose of phenolphthalein given to the cats does not get into solution at all, owing to the poor solvent powers of their intestinal juices. We, therefore, proceeded to test this hypothesis by administering a liberal excess of activated charcoal, which was done in the following experiment:

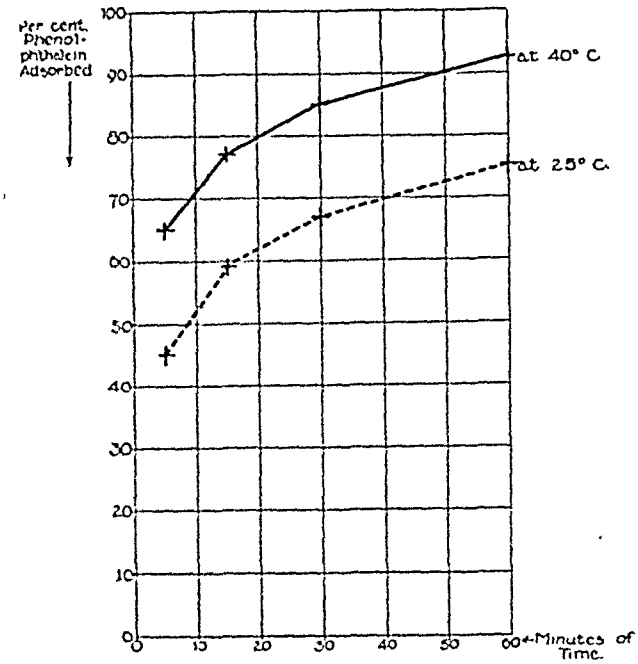
March 26, 1936, 11:30 a. m. Dose: 0.3 Gm. phenolphthalein followed by 5 gms. of Activated Charcoal (M) every two hours until 10:30 p. m. and another

Graph 3
Showing Amount of Activated Charcoal (N) Required to Adsorb 99.5% of 0.010 Gm of Phenolphthalein at Different Hydrogen ion Concentrations in 5 minutes at 25°C.



Graph III

Graph 4.
Showing per cent. Adsorbed from 0.040 Gm. of Phenolphthalein by 0.100 Gm. of Charcoal at pH 9.0 with Variation in Time and Temperature.



Graph IV

such dose at 8:00 a. m. next day. There was no laxative action the next day or the day thereafter.

CONCLUSIONS

1. Activated Charcoal of U. S. P. XI is a definite adsorbent for phenolphthalein, while Non-Activated Charcoal is almost devoid of this effect.
2. The adsorptive power of the charcoal is increased by diminution in degree of alkalinity, by increase in temperature and in the time of exposure.
3. Activated charcoal is capable of antagonizing the cathartic action of phenolphthalein in the cat when given in five times the dose necessary to produce the laxative action.
4. In the human, a considerably larger excess of activated charcoal is required; but, when such is given, the cathartic action is inhibited.

It seems probable that this new official preparation (Carbo Activatus) will be found much more effective than the formerly official form for various therapeutic purposes and that it may reinstate charcoal in the favor and confidence of the discriminating physician. Renewed studies of the therapeutic value of the new charcoal are decidedly in order.

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SECTION VII—*Surgery of the Lower Colon and Rectum*

Superior Peri-Rectal Abscesses*

By

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A BRIEF review of the anatomy of the superior peri-rectal space will help us to obtain a clear conception of the etiology and pathology of inflammations in this area.

The rectum passes through this space from above downward; the space is bounded by the pelvic peritoneum above and the levator ani below; the rectum in this space is surrounded by a fibro cellular layer of tissue through which ramify the arteries, veins and nerves before they penetrate the walls of the bowel.

*From the Department of Proctology, Jefferson Hospital.
Submitted February 26, 1936.

This space is subdivided into the posterior or the retro-rectal space and two lateral spaces anterior to the rectum known as the superior pelvi-rectal spaces. The blood vessels in the retro-rectal space are branches from the middle and lateral sacral arteries also a few from the inferior mesenteric. Those in the superior pelvi-rectal spaces come from the hypogastric artery. The lymphatics of the two spaces are also comparatively distinct: those in the retro-rectal space develop around the lower posterior portions of the rectum and coccyx, while those in the anterior spaces originate in the wall around the prostate, neck of the bladder and the uterine organs and connect with the iliac plexus and lateral trunks of the lymphatic system.

With such distinct anatomical divisions, vascular supply and lymphatic distribution, one can clearly understand why a distinction is made between the circumscribed inflammations in these two areas and distinguish them as retro-rectal and superior pelvi-rectal abscesses.

The retro-rectal abscess develops in the space between the sacrum and the rectum. It may be due to necrosis of the pelvis, sacrum, coccyx, ileum or vertebrae, to a foreign body in the bowel or the passage of bougies and hard rubber syringe tips. The operation of posterior proctotomy where complete drainage is not secured, is a frequent cause.

Strictures and fistulous tracts of the rectum, gummata, tuberculous lymphoid nodules and infection carried along the lymphatic channels from ulceration of the rectum above the external sphincter are other causes.

SYMPTOMATOLOGY

The early symptoms are vague and obscure. Usually they are not ushered in by a distinct chill. A dull ache in the sacral area with pains along the course of the sciatic nerve, malaise and constipation, with or without pain on defecation. Seen early, palpation externally around the perineum, as a rule does not elicit any pain or induration, there will be no fluctuation or tension. As suppuration increases, palpation with the gloved finger in the rectum will at times reveal marked pain, enlarged lymphatic glands a small abscess bulging into the lumen of the bowel or a diffuse boggy mass in the hollow of the sacrum, accompanied by a marked increase in temperature at this point.

The bowel may be partially obstructed and difficulty in micturition will develop. A blood count with an increased leucocytosis and an increase in the polymorphonuclears will be confirmative evidence of an abscess.

An X-ray film, where the cause is a bone lesion, will aid in the diagnosis.

Eventually an abscess may rupture spontaneously into the rectal cavity; it may also perforate the levator ani into the ischiorectal fossae and finally open through the skin.

TREATMENT

Such consists in drainage as early as possible to prevent rupture into the bowel. A slightly curved incision between anus and coccyx is best. This should reach to the levator muscle. With the index finger in the rectum as a guide, a bistoury is then passed with the cutting edge away from the bowel, through the levator muscle cutting at right angles to its fibres to facilitate free drainage. The remainder of the dissection is best done with the finger, increasing the size of the opening in the muscle and evacuating the cavity.

Curetting is not generally advisable on account of the possibility of perforating the superior pelvi-rectal spaces or rectum. A large size rubber drainage tube is introduced and held in position by a suture or adhesive strip at the skin margin. The sphincter should be stretched and the bowels kept regular, but not loose during convalescence. The wound should be irrigated through the tube twice daily for the first week with a glass syringe, using 1-2000 bichloride solution, a 1-2000 metaphen solution or a 2 per cent amphyl solution. No packing used after the first dressing at time of operation. As soon as possible get the patients on their feet for a short period daily, this facilitates drainage by gravity and by pressure of the abdominal contents above. Sitting should not be allowed until healing is well advanced.

Where the abscess has ruptured into the bowel previous to the patient being brought to operation; the function of the bowel will be best preserved by using the so called *seton*. This may be a silk or rubber band. It is inserted through the outside dissection and through the internal opening into the bowel, brought down and out through the external sphincter muscle and tied.

The tension of this *seton* is so regulated that it cuts slowly through the tissues from above downwards allowing the healing to keep pace with the cutting.

This procedure will usually require from four to six weeks, depending upon the patient's general health.

SUPERIOR PELVI-RECTAL ABSCESSES

These usually do not have their origin primarily from inflammation of the rectum but from surrounding organs, as the bladder, prostate, urethra, uterus, broad ligaments. Psoas abscess, necrosis of the pelvic bones, suppuration of the broad ligament, vesiculitis, perinephritis, and appendicitis may all cause an abscess in the superior pelvi-rectal spaces. Injuries in the anterior wall of the rectum, traumatism from labor, instrumentation of the urethra or uterus, operations for removal of stones in the bladder, prostatectomy and uterine tumors have all been known to cause these abscesses.

The chief causes however are infections of the prostate, seminal vesicles, uterus and broad ligiments. They usually begin with chill, fever, increased pulse rate, deep aching pain and urinary disturbance. Occasionally they develop slowly with very slight chill and slight fever.

Where the inflammation is tuberculous the symptoms will be less marked and the progress slower. In gonorrheal infections, the temperature may become very high and the constitutional symptoms alarming. The abscesses have a tendency to burrow outward toward the abdominal wall because of there being less resistance in this area than toward the perineum. A localized peritonitis may occur or they may perforate the peritoneum and death occur from acute septic peritonitis.

Perforation of other organs, bladder or rectum may also occur during the course. A sudden discharge of much pus through the bladder or rectum with relief

of pain and distress would indicate this; perforation of the vagina is rare.

A *diagnosis* of superior pelvi-rectal abscess rests largely upon diseases of the genito urinary and reproductive organs; rarely is there a history of previous rectal disease. Peri-anal or perineal palpation elicits deep tenderness but no swelling or induration. Rectal palpation will generally reveal a tenderness above and to one side of the prostate in the male; when the abscess has existed for some time it may become quite tense and burrow downward between the rectum and the prostate, perforate the levator ani muscle or penetrate the retro-rectal space.

It is in the early period of this inflammation that one finds it difficult to make an exact diagnosis and an early diagnosis is important in view of the grave complications which may arise from delay. The urinary symptoms often mask the rectal symptoms in men. In women these symptoms are generally taken to indicate an inflammatory condition of the uterine organs and a vaginal examination is soon made revealing the true nature of the inflammation.

In men as a rule these abscesses are situated anterior to and to one side of the rectum, they may be on a level with the prostate or just above it. In women they are more likely to be found to one side than anteriorly because the pelvi-rectal spaces are separated in front by the close union between the rectum and the vaginal wall below, and also because the lymphatics run along the borders of the broad ligament and therefore the infection is distributed along the sides.

These abscesses occasionally surround the rectum and destroy all the cellular tissue between the peritoneum and levator ani. They may perforate the levator ani and enter the ischiorectal fossa or the retro-rectal space. Those perforating into the ischiorectal fossa may later open through the skin in the anal region.

In cases where there has been much destruction of tissue around the rectum, there is not much prospect of restoration of perfect function of these parts. In the early stages it may be nearly impossible to diagnose these abscesses, though the general symptoms may indicate pus formation.

A blood count with marked leucocytosis would strengthen the indication of a developing abscess. Sigmoidoscopic examination or passage of rubber bougies would be contra-indicated on account of the danger of rupturing the abscess into the rectum.

TREATMENT

This consists in evacuating the abscess at the earliest possible moment and affording wide free drainage. The abscess should be opened by a deep dissection through the perineum. It is rarely justifiable to open it through the rectum, as it usually further complicates a serious condition. When the abscess cavity has been reached by the dissection, the use of the finger in blunt dissection is advised; there will be less injury of the large blood vessels and nerves and less possibility of rupture into the peritoneal cavity. A large rubber drainage tube is then inserted and fixed to the skin margin. The cavity should be thoroughly evacuated by irrigation with normal salt solution. The sphincter muscle should always be divulsed so that gas and fecal matter can pass easily, avoiding any additional strain to the weakened tissues separating the abscess from the rectum. If the urethra or bladder has been perforated by the abscess the conversion of the abscess into a perineal-urinary fistula will be the safest and surest means of securing a cure. In the after treatment rubber drainage tubes are preferable to gauze. No packing is used; after forty-eight hours a smaller tube may be inserted; this should gradually be shortened and removed entirely when the cavity has been sterilized. For irrigation a 1-5000 solution of bichloride of mercury, a 1-2000 solution of mercurophen or a two per cent solution of amphyl may be used. Irrigate two to three times a day for the first week, gradually reducing the frequency as the cavity clears. Get the patient on his feet as soon as possible to favor drainage.

CASE REPORT

The following history will illustrate the superior pelvi-rectal variety of abscess: A. C., age 53, a fisherman, Swedish ancestry, began having pain three weeks previous to time when first seen. He had consulted a surgeon who diagnosed and operated upon a superficial fistula in ano. At that time an enlarged prostate was diagnosed which was giving marked urinary symptoms. The day following the fistula operation, the patient complained the pain for which he had entered the hospital had not been relieved, became dissatisfied, signed a release and went home.

I saw him five days later when he had developed a retro-rectal abscess which protruded into the lumen of the bowel. The prostate was enlarged and firm and tender on palpation. No fluctuation noted. He was removed to the hospital on same day. On proceeding to drain the abscess it was found it had ruptured. It was drained by an external incision between the anus and coccyx, drainage tube inserted and he felt much but not entirely relieved. A polyvalent serum was then started to promote more rapid healing of the cavity.

Six days later he developed a pain in inguinal region and testicles; this was followed by a rise in temperature and painful area in right iliac fossa. Two days later there was a profuse discharge of pus through the drainage opening of the retro-rectal abscess. Under gas anesthesia it was found a prostatic abscess had ruptured through the superior pelvi-rectal space and into the drainage tract of the retro-rectal abscess. This was opened by blunt dissection, a rubber drainage tube inserted. A prompt cessation of all prostatic symptoms followed, and an excellent result was obtained.

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Elbow Deformity of the Colon*

By

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ELBOW deformity of the colon may be described as a V-shaped angulation, formed by the close approximation of the cecum to the hepatic flexure, with no diminution of the usual length of the ascending colon.

The origin of the condition is primarily a developmental arrest. The caecum, ordinarily, reaches its final position in the right iliac fossa by passing through two stages. It makes its appearance about the third week of foetal life, outside the body cavity. During the seventh week, it is drawn into the coelum and undergoes rotation to place itself over the right kidney. Thence, it grows downwards into the right iliac fossa. Subsequently, when all the abdominal viscera have achieved their normal habitats, a physiological peritonitis occurs. This results in the formation of adhesions whereby portions of the colon are fixed. Surgically, this is of the greatest importance, since by separating the adhesions, any fixed portion of the gut may be mobilized with its mesentery.

This high position of the caecum possesses advantages and disadvantages. The advantages are that the arrest in position corresponds with a halt in the development of the caecum which tends to remain small. This in turn obviates that form of constipation and its toxic concomitants which are associated with an overdeveloped caecum.

The disadvantages of the position are that the long loop of gut, suspended on a mesentery with a short base, is peculiarly susceptible to accident. The most common one is obstruction of the ascending colon, which is usually partial, but may be complete. The cause may be acute angulation, torsion, or obstruction by a band.

SYMPTOMATOLOGY

The most common symptoms of the condition in their approximate order of frequency are:

1. *Constipation,* pain and auto-intoxication.

These symptoms are produced by a delay in the fecal movement through the ascending colon. This is a mechanical effect of the acute angulation described as elbow deformity. The delay may range from a slight halt to a complete obstruction and the symptoms are commensurate with it. The pain is due to the drag of the loaded colon upon its mesentery.

2. *Regular epigastric pain and vomiting.*

Peptic ulcers are frequently simulated by this condition. The origin of the symptoms is a narrowing of the lumen of the duodenum or distal portion of the stomach. This may be the mechanical result of an adhesion between these viscera and the ascending colon or may be a reflex spasm from the same cause. Obviously, this may be a very difficult condition to diagnose. The delay in emptying time of the stomach with accompanying change in the gastric chemistry, distortion of the duodenal cap, etc., all point to some change in the lumen, and the erroneous conclusion that the change is either within the lumen or within the wall of the gut, rather than a force acting outside the wall.

If the condition is suspected, an opaque enema usually confirms the diagnosis.

3. *Back-ache, fatigue,* pain resembling Deitl's crisis, or stone in the ureter.

These symptoms are caused by adhesions over the kidney or ureter. The resultant tension may be slight and constant or strong and periodic. In this position, the adhesions are over the ilio-hypogastric and ilio-inguinal nerves and reflex manifestations may appear throughout their course. Common among these are frequency of micturition and pain in the anterior part of the perineum. Sharp spasms may be due to torsion of the pedicle.

4. *Flatulent dyspepsia,* sub-costal pain, pruritus and frank jaundice.

These symptoms are due to involvement of the gall bladder or biliary ducts in adhesions to the ascending colon. Again, the diagnosis is rendered difficult, since the most common causes of these conditions are mechanical obstruction within the lumen or malignancy without. Skiagrams are not of positive assistance but may yield negative information of value.

Very commonly, one or other of these syndromes exists in such a mild degree that the busy practitioner is unable to make a clinical diagnosis and is loathe to expend large sums of the patient's money upon chemical and radiological investigations. Frequently, the cases are labelled chronic appendicitis and referred to a surgeon. For various reasons, the appendectomy is often performed through a niggardly incision, no exploration is made, the condition is unrecognized, and the symptoms persist. The cost of an opaque enema is slight and it usually affords a rapid diagnosis. The disadvantages of an incision suitable for exploration are usually negligible.

Treatment of the condition is, of course, surgical. The technique utilizes a laparotomy incision, through which a thorough exploration is made. All adhesions are freed. The outside leaf of the mesentery of the caecum and ascending colon is opened throughout its length. Its contents are gently spread out. The caecum

*From Lynch Clinic, New York, N. Y.
Submitted April 23, 1936.



Fig. 1. Elbow deformity with post-caecal appendix and transverse band from caeco-sigmoid to mesentery.

and ascending colon are sutured into their proper position and so obliterate the slit in the mesentery.

CASE REPORTS

Histories of patients with these syndromes are appended and it is noteworthy that in this brief series there are two cases in which a previous appendectomy had failed to relieve the symptoms. The grouping has been made according to the prevailing symptoms, rather than the actual diagnosis.

Case No. 3821

1. *Mr. F. G.*, age 23. Salesman.

Symptoms—One year.

Family history—Mother died of cancer.

Past history—No serious illness.

Present history—Pain in right side, constipation.

Urinary history—Negative.

Physical examination—Some tenderness in right lower quadrant. Otherwise negative.

X-ray—Chronic appendicitis.

Pre-operative diagnosis—Same.

Findings—Chronic appendicitis, long and tortuous. Elbow deformity of colon.

Operation—Plication of caecum and appendicostomy (July 10, 1934).

Case No. 4402

2. *Mr. H. B.*, age 34.

Family history—Negative.

Past history—Typhoid fever at 10 years.

Present history—Pain in the right side in region of appendix for five weeks. Sharp pain at first, dull pain last two weeks. No vomiting.

Pre-operative diagnosis—Elbow deformity and chronic appendicitis.

Postoperative diagnosis—Same.

Findings—The appendix was running parallel to and adhered in one place to the right border of the liver. The ascending colon was undescended and there was no caecum. The ascending colon was turned in horseshoe form, the opening being toward the anterior abdominal wall.

Operation—Plication of caecum and appendectomy (March 13, 1925).

Case No. 4477

3. *Miss K. S.*, age 24. Law Student.

Past history—Negative.

Present history—For two years had pain in right lower quadrant radiating down thigh, nausea, vomiting and constipated.

Physical examination—Tenderness over McBurney's point and palpable caecum.

X-ray—Chronic appendicitis and bands across ascending colon and transverse colon causing partial obstruction and tremendous dilatation of colon and caecum.

Pre-operative diagnosis—Elbow deformity and chronic appendicitis.

Postoperative diagnosis—Same.

Findings—Acute angulation due to bands and chronic appendicitis.

Operation—Plication and appendectomy (1925).

Case No. 3973

4. *Miss R. D.*, age 29.

Past history—Negative.

Present history—Epigastric pain, no vomiting. Some nausea, eructation, appetite—poor, constipated. Stools—normal. Lost 30 pounds in six months. Some night sweats.

Physical examination—Caecum palpable and tenderness over McBurney's point.

X-ray—Inflammation of caecum and colon, possible tuberculosis.

Pre-operative diagnosis—Tuberculosis of ileum and caecum.

Postoperative diagnosis—Elbow deformity.

Findings—Marked elbow deformity of the ascending colon and long appendix. Cyst of left ovary.

Operation—Appendectomy and plication of caecum.

Case No. 2988

5. *Mr. E. M.*, age 35.

Past history—Negative.

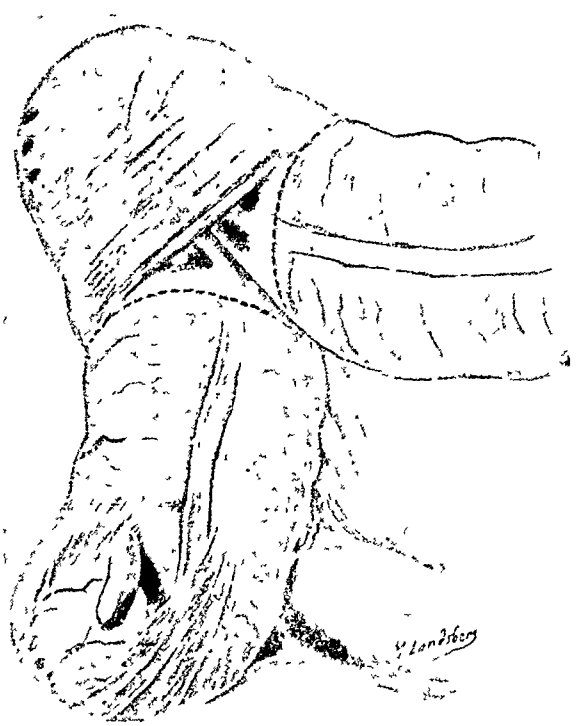


Fig. 2. Elbow deformity with cuff inclusion and post-caecal appendix.

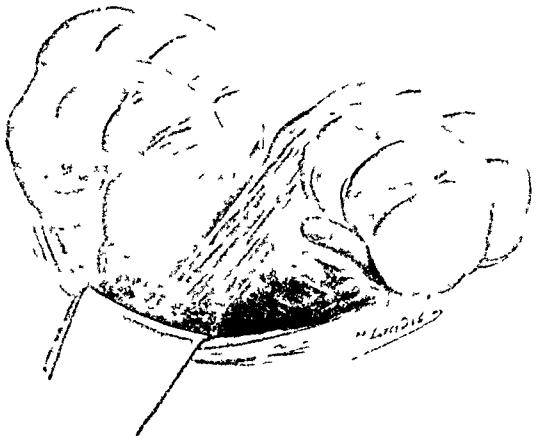


Fig. 3. Elbow deformity with lateral band from caecosigmoid to mesentery and post-caecal appendix.

Present history—Gastric pain relieved by food. No vomiting. Some eructations. Constipated.
X-ray—Chronic appendicitis.
Physical examination—Tenderness in right iliac fossa referred to epigastrium.
Pre-operative diagnosis—Elbow deformity and peptic ulcer.
Postoperative diagnosis—Elbow deformity and chronic appendicitis.
Findings—Elbow deformity and chronic appendicitis with adhesions to anterior wall.
Operation—Plication and appendectomy.

Case No. 4223

6. *Mr. W. C.*, age 23.
Past history—Negative.
Present history—Epigastric pain, vomiting and diarrhea relieved by vomiting. Intermittent attacks for five years. Flatulence marked.
X-ray—Duodenal ulcer.
Pre-operative diagnosis—Duodenal ulcer and elbow deformity.
Postoperative diagnosis—Chronic appendicitis and elbow deformity.
Findings—Adhesions to stomach, gall bladder, pylorus, caecum and colon. Base of infantile appendix adherent to gall bladder.
Operation—Freeing of adhesions, appendectomy, resection of 3 inches of ascending colon (1925).

Case No. 4215

7. *Mr. G. W.*, age 31.
Past history—Negative.
Present history—Bouts of epigastric pain relieved by food for 8 years. No nausea, no vomiting, constipated.
X-ray—Negative.
Pre-operative diagnosis—Duodenal ulcer, chronic appendicitis and adhesions.
Postoperative diagnosis—Elbow deformity, adhesions and chronic appendicitis.
Findings—Colon adherent to gall bladder, pylorus and omentum. Elbow deformity.
Operation—Adhesions freed, appendectomy, and plication of caecum (1925).

Case No. 4259

8. *Miss M. C.*, age 26.
Past history—negative.
Present history—Epigastric pain relieved by food. Vomiting. Pain 2 hours after food. Flatulent.
Physical examination—Tenderness over right lower quadrant.
X-ray—Chronic appendicitis and adhesions.
Pre-operative diagnosis—Elbow deformity and chronic appendicitis.
Postoperative diagnosis—Same.
Findings—Ascending colon adherent to liver. Elbow deformity.
Operation—Plication of caecum. Appendectomy and freeing of adhesions. A portion of liver was removed.

Case No. 595

9. *Mrs. M. H.*, age 26. Nurse.
Family history—Negative.
Past history—Measles, scarlet fever, typhoid fever, rheumatism, diphtheria, pneumonia and appendectomy.
Urinary history—Micturition 1-3 times daily.
Present history—Pains, onset in back, radiating to right groin, intermittent fever, colicky attack lasted 15 minutes. Bloody urine, not constipated, vomited on this attack. Has had attacks before but no severe pain. Urinary history at times every hour daily.
Cystoscopic examination—Negative. Dr. J. Bently Squier ruled out urinary pathology.
Pre-operative diagnosis—Elbow deformity of the colon.
Postoperative diagnosis—Same.
Findings—On opening the abdomen, a very large, dilated, non-fused caecum appeared in the wound. The right kidney was examined and found contracted. There was also slight constriction of the lower pole of the right kidney but the left kidney was somewhat larger than the right. All organs were found normal except for a *marked elbow deformity of the colon.*
Operation—Plication of the caecum by Dr. Lynch, October 22, 1920. All symptoms cleared up within 12 days.

Case No. 4226

10. *Mrs. R. S.*, age 32. Housewife.
Symptoms—One year.
Family history—Negative.
Past history—No serious illness. Previously operated upon for removal of uterus, left ovary and appendix.
Present history—Pain in right iliac fossa. Pain, sharp, radiates to back. Constipation severe. Pain has no relation to food. No nausea or vomiting.
Urinary history—Slight frequency of urination during attacks.
Physical examination—Tenderness in right iliac fossa. Palpable caecum. Moveable right kidney.
X-ray—No abnormality of urinary tract.
Pre-operative diagnosis—Cystic right ovary and elbow deformity.
Postoperative diagnosis—Same.
Findings—Cystic right ovary and dilated flappy caecum, also one band of adhesions causing elbow deformity of ascending colon. Stomach and gall bladder—normal.
Operation—Punctured ovarian cyst and plicated cecum (Jan. 13, 1925).



Fig. 4. Elbow deformity showing funnel-shaped embryonic caecum.

Case No. 4314

11. *Miss C. H.*, age 26. Telephone operator.

Symptoms—One year.

Family history—Father died of cancer.

Past history—No serious illness.

Present history—Pain in R. L. Q. during menstrual periods for 1 year but for the past week pain was between periods and accompanied by vomiting. Bowels constipated.

Urinary history—Burning and pain for last week.

Physical examination—Negative except for some tenderness over McBurney's point.

Pre-operative diagnosis—Subacute appendicitis.

Postoperative diagnosis—Chronic appendicitis, elbow deformity and non-fused colon.

Findings—Long appendix, adhered to lateral colic fold. Non-fusion of colon with common mesentery. Gall bladder and stomach—normal. Small cysts of both ovaries.

Operations—Appendectomy and plication of caecum (Sir Henry Gray technique (Feb. 10, 1925).

Case No. 4131

12. *Miss T. M.*, age 26.

Symptoms—2 years.

Family history—No chronic diseases.

Past history—No serious illness.

Present history—For past 2 years pains and burning in the stomach. Nauseated, sour stomach, no vomiting. Headaches. Belches a great deal. Lost 15 lbs. in weight. Constipated. Pains relieved at times by food.

Urinary history—Frequent desire for urination of late.

Physical examination—Negative except for tenderness over epigastrium and R. U. Q.

X-ray report—Moderate ptosis of stomach and small intestines.

Pre-operative diagnosis—Elbow deformity, chronic appendicitis and adhesions.

Postoperative diagnosis—Same, cholecystitis.

Findings—Chronic appendicitis and chronic cholecystitis and elbow deformity of colon. Gall bladder looked ashy gray and when cut open had typical strawberry appearance of chronic inflammation. The caecum was pigmented. Stomach normal, duodenum dilated because of elbow deformity of colon.

Operation—Cholecystectomy and appendectomy and plication of caecum.

Case No. 4276

13. *Mrs. C. C.*, age 50.

Symptoms—Constipated all her life.

Family history—Father died of Bright's disease; mother died of apoplexy.

Past history—No serious illness.

Present history—Constipated and troubled with indigestion all her life. Three years ago severe attacks of pains in R. U. Q. Pains radiated to the back in both sides of the spine. Vomitus—green. Slight fever, became jaundiced 3 days later. Similar attacks 3 or 4 months but no jaundice. Constant pain for past 5 weeks. Passes a good deal of mucus by bowels, stools never clay colored.

Physical examination—Negative except for tenderness over McBurney's point and gall bladder region.

Urinary history—Negative.

X-ray—

Pre-operative diagnosis—Chronic appendicitis and chronic cholecystitis.

Postoperative diagnosis—Elbow deformity, chronic appendicitis and adhesions.

Findings—Dense adhesions about gall bladder—adhesions binding caecum to parietal peritoneal wall near hepatic flexure of colon. One strong band of adhesions from anterior longitudinal band near caecum to hepatic flexure of colon. Another band of adhesions from ascending colon to gall bladder. The caecum was of the flappy, dilated type. The stomach and sigmoid appeared normal. Small chronically inflamed appendix.

Operation—Freeing adhesions, appendectomy and plication of caecum.

Case No. 4225

14. *Mrs. E. R.*, age 36. Clerk.

Past history—Negative.

Present history—Pain in the stomach about 2 hours after going to bed, wakes her up. Steady pain. Belches. Forced vomiting, which relieves her. Brown fluid. Bowels constipated. Cascara every night. Feels like eating but is afraid to eat meats, etc.

Urinary history—Negative.

Physical examination—Negative except for tenderness over the descending colon.

X-ray examination—Shows the presence of a partial obstruction in the upper half of the second portion of the duodenum, apparently due to adhesions between the gall bladder and the adjacent viscera. The rest of the second portion of the duodenum was slightly dilated and there was a moderately delayed motility there. The appendix, too, was apparently chronically inflamed with apparently ileocecal adhesions.

Pre-operative diagnosis—Chronic cholecystitis, chronic appendicitis, adhesions and elbow deformity.

Postoperative diagnosis—Elbow deformity, chronic appendicitis, attic adhesions and small multiple fibroid uteri.

Findings—Chronic appendicitis, flappy, dilated caecum and elbow deformity of ascending colon. Few fine adhesions around duodenum. Uterus had several small fibroids.

Operation—Freeing adhesions, appendectomy and plication of caecum.

Annual Abstracts of Proctologic Literature

(May, 1934-May, 1935) By CLEMENT L. MARTIN, M.D., Chicago, Illinois

The complete bibliography from which these Abstracts were made will be published in full in the Transactions of the American Proctologic Society, 1935.

LYMPHOGRANULOMA INGUINALE

For a brief description of this disease see Transactions 1933-1934, more detailed ones will be found in Hellerstrom's monograph, in *Cole's* paper, *J. A. M. A.*, 101:1069 (Sept. 30), 1933, and *Fischl's* article and others cited in this and previous bibliographies.

Synonyms: Lymphopathia venerea, *Nicolas-Favre-Durand* disease, climatic bubo, tropical bubo, hypertrophic bubo, non-venereal bubo, strumous bubo of the groin, subacute inguinal paradenitis, "fourth" venereal disease, non-tuberculous granulomatous lymphadenitis, subacute inguinal lymphadenitis; some, perhaps most of the cases of "hypertrophic and stensosing rectitis" described by the French, some of the cases of genito-anorectal elephantiasis, some, if not nearly all, cases of "esthiomene." It may be noted that ulcus vulvae acutum (Lipschutz) is a separate entity as is *"periadenitis mucosa necrotica recurrens."* O'Leary criticizes the use of the latter term; he regards it as synonymous with ulcerating aphthous stomatitis, a local disease, and classifies those cases with both vulvar and

mouth lesions as "ulcerative vulvitis and stomatitis, a systemic (disease)."

ETIOLOGY

There are few noteworthy additions to our knowledge of this disease to report this year. That the disease is a definite entity and the Frei test is specific have been established in the past; various current articles confirm this. That the disease is caused by a filtrable virus is generally but not universally accepted. Levaditi, Ravaut, *et al*, determined that the serum of patients with the disease neutralizes lymphogranuloma inguinale virus *in vitro*. Grace and Suskind succeeded by intracerebral inoculations of mice in transmitting the virus through 35 generations (sub-inoculations), with marked increase of its virulence and thus prepared an active mouse-brain antigen. The Reviewer has found it more potent than most of the antigens prepared from suppurating inguinal glands, but it may give false positive reactions.

THERAPY

There would be a clearer concept of therapeutic possibilities in the proctologists field if certain facts emphasized by Collier Martin, among others, generally were known and appreciated. Dr. Martin notes that it is chiefly a Negro disease, best described as "incurable" thus far; that it expresses itself as a rectal stricture in the female, and that its prominent feature in the male is an inguinal adenitis following a primary sore on the penis, the adenitis frequently suppurating. Fifteen of his cases . . . . "all had massive peri-rectal deposits of inflammatory tissue with marked contraction of the lumen of the bowel and multiple rectal and peri-rectal infections with fistulas involving the peri-anal area."

It is hardly to be expected that most of the medicinal agents used and advocated for this disease could exert much effect on the tubular strictures and dense scar tissue we find in these patients. Dilatation with bougies, cautiously done, posterior linear proctotomy and, in the more advanced cases, colostomy, have definite value in the treatment of the rectal stricture.

Conservative surgical measures, *i.e.*, incision and drainage of peri-anal abscesses and curettage or the swabbing out of sinuses which may be readily explored, is helpful in some cases. The Reviewer does not hesitate to perform a fistulectomy on these patients if the internal orifice is at the muco-cutaneous juncture; they are benefited and the wound heals. Fistulectomy is indicated only in the exceptional case, however. Antimony and potassium tartrate continues to have advocates: 5 c.c. of a 1% solution given intravenously twice a week is the usual dose. Rainey gives 3 c.c. for the first dose and increases this up to 7 c.c. on the 5th dose if it is well tolerated, dosage is then maintained at 7 c.c. Intradermal injections of 0.1 c.c. of antigen twice a week, as advocated by Pilot, are being given in a number of cases. It is still too early to determine their value, but my own results are not encouraging.

My experience with any medication in this disease has not been encouraging. For the inguinal adenitis, roentgenotherapy is used by some authors; after suppuration occurs, simple incision, curettage or gland excision is variously practised. Weeks advocates radical excision of enlarged and suppurating glands. Hot moist dressings are then commonly applied.

Thomas and McCarthy report favorably on the use of a bouillon filtrate applied as a wet dressing to the suppurating glands.

MEGACOLON

Bonar designates as "pelvi-rectal achalasia" that type of Hirschsprung's disease apparently caused by failure of relaxation of the musculature at the pelvi-rectal flexure. A case is reported of a boy 3 years of age with this dysfunction who was treated by repeated intrarectal injections, of a saturated solution of magnesium sulphate. In the course of two years over 200 satisfactory bowel movements were obtained, abdominal distention was reduced, and nutrition and health were decidedly improved. While surgical division of the sympathetic nerve supply to the large bowel is the treatment of choice, Bonar suggests that the age and condition of the patient often makes preliminary medical treatment necessary, and, the procedure described may be a valuable adjunct, if his results are confirmed.

NEOPLASMS

The relation of polyps to rectal cancer continues to be investigated. The most careful and worthy work in the last year with which I am familiar is that of *H. Westhues*. His book 'The Pathologico-anatomical Basis of Surgery for Rectal Carcinoma" is reviewed in the December issue of the American Journal of Digestive Diseases and Nutrition. Although I do not fully agree with his classification of polyps, his material is different from my own and his findings are supported by much data.

Bargen and Dixon report on uncommon tumors in the large intestine. They found reported in the literature fibroma, fibromyoma, fibromyxoma, fibromyxangioma, adenofibromyoma, fibroleiomyoma, myoma, adenomyoma, angioma, lipoma, cholesteotoma, paraffinoma, taratoma, glioma, dermoids, and cysts. They report a case of fibroma in the cecum and one of myosarcoma of the rectum. They advise surgical treatment in all these conditions.

Coccyxgeal dermoids are discussed by *Ferrari and Meyer-Burgdorff*. *Fletcher, Woltman and Adson* present a study of sacrococcyxgeal chordomas.

In his paper on rectal polyps *David* makes the points that a biopsy specimen from the base of the tumor is necessary, that the slightest evidence of ulceration or induration are suggestive of malignancy, and that the pathologist must have a history and definite idea of the tumor's gross appearance and the proper section for a diagnosis.

Newton Smith concludes that rectal polyps are comparatively rare in infancy. When they do occur they seem to grow rapidly and should be removed.

Poston reports an acute intussusception caused by a lipoma in an adult. *McKenney's* paper epitomizes current concepts of colon neoplasms. *Kuru* reports a lymphosarcoma of the rectum. *Read* performed a successful colon resection in a five year old child for a solitary adenomatous polyp which had caused recurrent intussusception. In a case of my own not yet reported, a single adenoma 2 x 2½ cms. was excised from the upper sigmoid by colotomy, recurrent partial obstruction but no intussusception preceded the operation. The child recovered.

Bowman describes a villous papilloma of the rectum with early malignancy, a rare benign tumor which undergoes malignant changes in 12 to 20% of cases. It should be removed when found. It has struck me that these papilloma resemble very closely intravesical papilloma.

OPERATIONS

See titles Prolapse, Sympathectomy, etc., for certain special subjects.

Stetten presented a 38 year old woman with post operative incontinence of 9 months duration who had a satisfactory result after approximation of the separated sphincter ends. The usual procedure was done through a crescentic skin incision.

When incontinence has followed a fistulectomy *Collier Martin* advocates excision of the depressed gutter which extends into or through the anal canal, together with the immediately adjacent scar tissue. Free dissection is avoided. If there has not been too great an interval between the fistulectomy and the operation for incontinence, repair and return of function may result.

Valentine and Rogers report a case of recto-urethral fistula with involvement of the prostate and right seminal vesicle in a 40 year old man who gave a history of repeated catheterizations for urinary retention over a 6 month period when a 5 year old child. At the end of this period

there was a spontaneous discharge of pus through the rectum after which he voided voluntarily. He married at 24 and thereafter had attacks about every three or four years of a feeling of fullness and swelling in the rectum, accompanied by hematuria. At operation the prostate and seminal vesicles were exposed through the usual perineal incision. The space between the rectum, urethra and bladder was occupied by much dense fibrous, inflammatory tissue. This area with "at least a portion of the fistulous tract" was removed and the right lobe of the prostate further incised for drainage. An indwelling catheter was anchored in the bladder and left 7 days. After its removal a little urinary leakage came through the wound for a few days but it then healed firmly. His present condition is satisfactory in all regards.

Johnson describes his technic for repair of complete laceration of the perineum. He states "most textbooks picture the external sphincter muscle as a fat circular band of voluntary muscle fibers . . . (but) actually it can be dissected out, in its major portions, as two elliptical flat muscle bellies about 10 cms. long and 2 cm. wide, with tendinous origins at the ano-coccyxgeal ligaments and tenninous insertions into the central tendon of the perineum; in other words, the main portion of the sphincter ani externus is composed of two independent, almost parallel muscles including the anus between them. The dimple at the sight of the tear is not only scar tissue but the torn fascial and tendinous insertion of the sphincter muscle belly." He approximates the torn sphincter ends by a through and through No. 4 catgut suture embracing skin and muscle, ties this and then stretches the muscle with a rectal dilator. He then removes this suture and does a perinorrhaphy (*Barrett*).

Note that Milligan and Morgan (Anatomy, Transactions, this issue) give a different description of the external sphincter.

Colostomy. Gabriel discusses colostomy based on a study of 970 cases. The chief immediate causes of death are: cardiovascular and pulmonary complications, peritonitis, paralytic ileus, prolapse of small intestine, and mechanical obstruction. Stenosis of the colostomy opening is the most frequent late complication. Fixation of the colon with obliteration of the lateral space and immediate opening of the colostomy are stressed in the operative method.

Dennick reviews colostomy from its birth in 1793 by Duret and covers its evolution through the posterior approach and up to the present types. Two methods are now recognized, the spur type and division of the bowel with invagination of the distal end.

R. Best prefers the paramedian incision because muscle to muscle and fascia to fascia approximation give better support to the wound and where colostomy is indicated provides a better functioning colonic aperture. A number of interesting operative details in colostomies are described.

Salvin reports a new operation for rectal prolapse consisting of fixation of the rectum to the previously ventrofixed uterus and to the abdominal wall. He claims avoidance of injury to ureters and iliac vessels and obliteration of pouch of Douglas.

SECTION VIII—*Editorial*

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastro-enterological Association is in no way responsible for editorial expressions.

ABDOMINAL PAIN DUE TO INTRACRANIAL DISEASE

GASTRO-ENTEROLOGISTS will be much interested in a recent article by Wechsler on "Abdominal pain as a symptom of disease of the brain."* Frequently physicians see men and women who complain bitterly of abdominal pain which does not correspond to the distribution of any particular nerve or spinal segment, and which is not associated with any demonstrable disease in any part of the digestive, the urinary or the genital tract. In many of these cases several operations have been performed, and appendix, gall bladder and parts of the pelvic organs have been sacrificed without avail.

Oftentimes the pain is said to be continuous day and night for year after year, and yet the patient commonly continues to look fairly well. This, together with the fact that years of suffering have not ended in death or disaster, must always cause the attending physician to suspect that the trouble is a "functional" one. But this doesn't help to relieve the pain! Another thing that sometimes makes the physician suspect that the pain is not due to disease in the abdomen is his discovery that even a large dose of morphine has no effect on it. If the pain were arising in a distended bile duct, ureter, or segment of bowel it would almost certainly be relieved or moderated by morphine. Similarly, such pains commonly fail to let up after the blocking of posterior roots or splanchnic nerves with procaine.

Sometimes the physician will decide that the pain must be psychic in origin, but this doesn't help much because, as Foerster has said, in the last analysis all pains are psychic; they are all perceived in the brain. Doubtless what the physician has in mind when he speaks of psychic pain is that the distress arises in the brain and is projected to the periphery. Perhaps it would help to look on some of these curious pains and burnings as hallucinations of sensation, comparable with those which cause a psychopathic person to feel sure that he has a snake or a frog in his stomach.

Whatever the cause, it is certain that in most cases the patient suffers, and often a life is wrecked. That the suffering is severe is indicated by the fact that so many of these patients welcome one major operation after another.

It is helpful now to have Wechsler's report of fourteen cases of abdominal pain in which the cause appears to have been a definite lesion in the brain. That such things are possible has been known for years, but there still is much need for the reporting of cases of this type.

According to Wechsler, the pain was often cramping; in the different cases it came in different parts of the abdomen, every quadrant being represented in the

*Wechsler, I. S.: Abdominal Pain as a Symptom of Disease of the Brain. *J. A. M. A.*, 105:647-650, 1935.

list of sites. In several cases it was accompanied by nausea and vomiting, and in several the thing that should have put the clinician on his guard was the fact that the abdominal disturbances came at any time without relation to the taking of food. In other cases a useless appendectomy might have been avoided if more attention had been paid to symptoms which pointed to the presence of intracranial disease.

This does not mean that all the puzzling and at present unexplainable abdominal pains are from the brain; all it suggests is that this possibility should be kept in mind everytime a healthy looking patient appears with pain which is not affected by exertion or by eating or by the cycle of activity in any one of the organs in the abdomen.

Walter C. Alvarez, Rochester, Minn.

SECTION IX—*Book Reviews*

(This section is open to contributions from any medical reader, whether or not a member of the Editorial Council).

Uber die Rhythmik der Leber-funktion, des Stoffwechsels und des Schlafes. By Erik Forsgren. Publisher, N. J. Gumperts Bokhandel, Stockholm, 1935. No. of pages 56. Origin, Sanatorium Svenshögen.

PART I of this review is a consideration of the rhythmic changes in the liver of the experimental animal, hitherto described in scientific journals. The author describes this periodicity and alternation of the assimilatory and secretory activities of the organ. The secretory phase of the cycle is accompanied by an increased diuresis, increased heat production and rise in body temperature.

There are no data that the kidney itself has any intrinsic rhythm of its own; such rhythm as it does manifest is probably dependent upon the rhythm of the liver.

When rabbits have full access to food, the author learned that the peak of the assimilatory phase occurred about midnight, or some time thereafter. Secretory activity became evident in the latter part of the night or early morning and became more marked in the forenoon. The assimilatory phase then began in the early afternoon and reached its peak again near midnight. Much variation was encountered among the animals studied and no clear line of demarcation was consistent for all.

Although there is plenty of food in the stomach, the liver cell gives up its glycogen as the organ enters the secretory phase of the cycle. Since at least twenty-four hours is required for the emptying of the stomach of the rabbit, the author believes that the twenty-four hour variation in the liver is really due to certain astronomic factors to which the organism is subjected and not to the food factor. The twenty-four hour day is an astronomic concept; most men and animals sleep at night, rising with the sun and pursuing their round of activity in keeping with this twenty-four hour concept. The author is of the opinion that since our sense of sight is controlled by the cerebrospinal nervous system, the liver is no doubt controlled by the action of the vegetative nervous system in some similar way. Then, too, he believes that the rhythm of the liver may well be stimulated or changed by the action of certain hormones. In other words the author believes that the rhythmicity of the liver is due to certain intrinsic factors which are set in motion by some extrinsic astronomic mechanism, and that food is not a factor in elaborating this cyclic phenomenon.

The Second Part of this report concerns the author's study of certain clinical cases. Although the liver plays the dominant *rôle* in controlling rhythmic phenomena in the body, the kidney reflects this hepatic rhythm although having none of its own. During the secretory or dissimilatory phase of the hepatic cycle there is increased diuresis, a flood of water with dissimilation products, and an increase in body temperature.

The first clinical case reported was that of a normal man, thirty years old, who remained in bed during the period of observation. Adequate meals were provided at 9 a.m., 1:30 p.m. and 9 p.m. Body temperature, total urine, and nitrogen, urea and urobilin were computed at two-hour intervals. In a second experiment comparable data were obtained but the patient was fed at 7 p.m., 12 m. and 5 a.m. during the night rather than during the day. Variation curves were plotted covering the changes in the items indicated above. In general the author believes that a twenty-four hour rhythm maintains irrespective of the time food was taken. Knowledge of hepatic rhythmicity explains the changes which occurred in the kidney. During the secretory phase of the liver cycle, water is given off, explaining early morning diuresis. During the assimilatory phase the liver takes up water, and this explains the decrease in diuresis after the evening meal. The twenty-four hour variation in the urea output coincides with the variation in protein metabolism in the liver.

Forsgren's observations anent cyclic activity in the glycogen-forming and bile-secretory functions of the liver have been confirmed in the main by other investigators, notably by Higgins and his associates. The latter are of the opinion that the author places too much emphasis upon extrinsic or astronomic factors in the elaboration of this cycle and not enough upon food. They feel that when the consumption of food is rigidly controlled, these cyclic changes, particularly those concerning total weight, glycogen, and content of water, are largely dependent upon physiologic factors associated with feedings.

George B. Eusterman, Rochester, Minn.

SECTION X—*After "Hours"*

Causae Mortis*

By

VIRGIL E. SIMPSON, M.D.
LOUISVILLE, KENTUCKY

DEATH IN LITERATURE

"AND all the days that Adam lived were nine hundred and thirty years, and he died."

Death is universal. No sex is spared, no age exempt. The majestic and courtly roads over which monarchs pass, the way that men of letters tread, the path the warrior traverses, the short and simple annals of the poor—all lead alike to the grave.

Poets, essayists and orators have made death the theme about which they have rhapsodied, philosophized and grown eloquent respectively. As a theme it has bulked large since the earliest times of recorded literature. Epictetus philosophized about it and wrote: "Since death be daily before your eyes, then you will never entertain any abject thought nor too eagerly covet anything." Longfellow with poetic license in beautiful phrase pictured it as but a gateway through which mortals pass:

> "There is no death; what seems so is transition.
> This life of mortal breath is but a suburb
> Of the life Elysian which we call death."

Socrates, as might have been expected, declined to be perturbed about it, as is evidenced by his injunction, "Be of good cheer about death; know this of a truth, no evil can happen to a good man either in life or after death." Shakespeare, like a sentient plummet sounding every human emotion and almost every phase of human interest, is not looked to in vain for some expression concerning death. Thus we find him saying:

> "Sense of death is most an apprehension,
> And the poor beetle that we tread upon
> Feels a pang when it dies as great as
> When a giant dies."

Bacon expressed a great thought, withal perhaps a true one, when he said, "It is as natural for man to die as to be born, and to a little infant perhaps the one is as painful as the other." Michael Angelo, as might have been expected, linked death to love, and said, "Death and love are the two things that bear the good man to heaven." Sir Walter Raleigh, perhaps between smokes, said:

> "Of death and judgment, heaven and hell,
> Who oft doth think must needs die well."

Pope looked upon it as a great release when he said, "Death is the liberator of him whom freedom cannot release; the physician of him whom medicine cannot cure; the comforter of him whom time cannot console." Wordsworth is sometimes quoted as having said the good die young; what he did say was, "The good die first; they whose hearts are dry as summer's dust burn to the socket." Menander had long before expressed the essence of such a thought when he exclaimed, "He whom the gods love die young." Wonder is sometimes expressed concerning the reluctance of the anchorite to die. Jay commented on this theme thusly, "A dislike of death is no proof of the want of religion. The instincts of Nature shrink from it, for no creature can like its own dissolution."

With something of the same thought in mind, Montaigne wrote, "It is not death, it is dying, that alarms me." I like what Sterne said about it, "Death opens the gate of Fame and shuts the gate of Envy after it." But of all, I think perhaps I like best the words of Daniel Webster, "One may live as a conqueror, a king or a majesty, but he must die a man." And as the great leveler of us all, one is reminded of the story of Alexander the Great, who, seeing Diogenes looking attentively at the parcel of human bones, asked the philosopher what he was looking for. "That which I cannot find," was his reply, "the difference between your father's bones and those of his slaves." From Cicero came a paean of resignation: "To me Death is even now desirable, after all the honors I have gained and the deeds which I have done." "I must die," says Epictetus, "but must I die sorrowing?" In Hebrews IX:27 one reads: "It is appointed unto men once to die, but after this the judgment."

The late Dr. Osler set aside one corner of his library to what he impishly called "Death, Heaven and Hell" corner. The books in this particular section, old and new, dealt with spiritualism, dreams, ghosts, witchcraft, longevity, premature burials, cremation, etc. Here, too, could have been found Maeterlinck "On Death," of which Osler said in a letter published later in the Spectator in 1912 that he had read with some eagerness Maeterlinck's essay, but that he was much disappointed. Quoting him, he said, "There is an unpleasant flavor, a cadaverous mustiness about the essay which even the words cannot cover, and in spite of a plea for burning burials, one smells everywhere the mold above the rose." And then further along in that same letter which was published in the Spectator, he protested against the pictures then extent which had

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been made of the act of dying. A few of those which he listed were, "The Pangs of Death," "The Awful Struggle," "The Sharpest Peak of Human Pain," "Tortures of the Last Illness." "The truth is," he said in commenting on these pictures, "that an immense majority of all who die, die as they are born—oblivious. A few, a very few, suffer severely in the body, fewer still in the mind." And then he quotes Shelley:

> "Mild is the slow necessity of death;
> The tranquil spirit fails in even breath.
> Without a groan, almost without a tear,
> Resigned in peace to leave this sphere,
> Calm as a voyager to some distant land,
> Full of wonder, full of hope, is he."

And further along he takes issue with what he calls a type of hysterical statement that all doctors consider it their first duty to protract as long as possible the most excruciating convulsions of the most hopeless agony. There are, he says, no circumstances contradicting the practice of Thomas Fuller's good physician, "When he can keep life no longer in, he makes a fair and easy passage for it to go out." "Nowadays," he says, "when the voice of Fate calls, the majority of men may, with Socrates, assert, 'I owe a cock to Asclepius.' A debt of thankfulness was his for a fair and easy passage."

Osler, it appears, always had a deep philosophical interest in the subject of death and soon after reading Munk's "Euthanasia" he wrote for the Canada Medical and Surgical Journal under date of March, 1888, the following, "We speak of Death as the King of Terrors, yet how rarely does the act of dying appear to be painful. How rarely do we witness agony in the last hour. Strict, indeed, is the fell sergeant in his arrest; few feel the iron grip; the hardest process of Nature's law is for most of us mercifully effective, and death, like birth, is but a sleep and a forgetting." He approves in that article of Munk's advocacy of the free but judicious administration of opium, not so much for the allaying of pain as for the relief from exhaustion,—of indescribable distress and anxiety—referred to the heart and stomach. Then he quotes Huseland, who declared 'Opium is not only capable of taking away the pangs of death, but it imparts even courage and energy for dying.'

It is said of Osler that though he suffered deeply in his last illness that he never permitted others to witness his suffering, that is, the evidence of his suffering. And Cushing says of him in connection with the loss of his only child that "he brushed his sorrow and his emotions aside with some remark which to the unknowing might have seemed almost flippant, "And if I laugh at any mortal thing 'tis that I may not weep."

"The doctors and the priests," said Napoleon, "have long been making death grievous." Well may one ask, how far correct was Napoleon? In every hospital one may witness the wreck of an accident or the victim of an infection hopelessly done for, but watch the doctor. He injects high-powered drugs into the tissues; gives glucose solution in a vein, starts a proctoclysis, fills the tissues with needles through which may gravitate normal saline. And then he rushes to the side of the stricken family and relates the story of his superhuman efforts, only to rush back to the bedside to futilely pump in the victim a serum. Why cannot the physician with a dignity in keeping with his place as a man of science, tell the family there is no hope, but that the dying shall go in comfort? Why cannot he in accord with old Seneca come to realize that the end of torture is the best part of that torture.

THE BIOLOGICAL ASPECTS OF DEATH

Shakespeare was pleased to divide the span of life into seven stages, but from a biological standpoint we can only make five divisions of the life cycle of individual multicellular organisms. Before considering these five phases of the life cycle, it is perhaps wise to consider the definition of some biologic terms. The word gamete means a sex cell, a cell that contains the parental inherited material, and since these are halved by a process known as reduction division, men say that a *gamete* contains one member of each pair of inherited factors. These inherited factors are called *genes*. When two *gametes* fuse, that is, the egg cell and the sperm cell, the result of this fusion is a fertilized egg cell, a cell that forms the starting point of a new organism, the name of which is the *zygote*.

The first phase of the life cycle, then, is the formation of the *zygote*. One may say that the life picture of the individual as a distinct biologic entity begins with this event. The second phase is the period of development and growth. This, naturally, can be divided into two sub-phases, (a) the embryonic or foetal phase and (b) the post-embryonic or post-natal phase. The duration of this growth phase of the life cycle of various kinds of multicellular organisms covers a wide difference, as for example, in the ordinary fruit fly this cycle is only about 8 days, whereas in man it covers about twenty years.

This, then, is succeeded by the third phase, the phase of adult stability, during which period there are no marked changes observable, either in the direction of growth or degeneration. Sometimes it is spoken of as "the prime of life." The duration, of course, is variable, but sooner or later the individual can be observed, even casually, to be beginning to pass into the fourth phase, which biologically is spoken of as the period of senescence. Here one sees evidences of the progressive waning in the intensity of the vital processes, along with the degenerative changes in the actual structure of the body. The duration of this cycle varies just as greatly as that known as the prime of life, but as Jeff de Angelis sang in that silly ditty, "A little bug'll get you some day," and sooner or later there comes an end to this phase, which introduces a final cycle in the life period of man, known as death. Of course, the individual life cycle may be terminated anywhere after the first phase has occurred, namely, the fertilization. Attractive as may be a consideration of the first three phases, we are particularly interested here only in the two last, the senescence and death.

The average period of the life cycle of the human family has been materially lengthened in the last two decades, or shall we say the last three decades. Thirty years ago, the average expectancy of human life was about thirty-four years of age; today it is well along beyond fifty-six. Attempts at explaining the variations of the life cycle of different species of multicellular organism have never been successful. As an illustration, at one time it was contended that the duration of an animal's life was somewhat in correlation with its size; as is well known, a parrot is much smaller than a horse and yet outlives it by many years. What is perhaps of greater interest and a more difficult solution is the individual variations of the life cycle in the

same species. Probably the most important influence in the difference between individuals, which finds expression in the varying degrees of longevity, are definitely inherited factors.

The statement that natural death is a novelty sounds rather unreasonable at first thought. Such a statement implies that neither senescence nor natural death is a necessary, inevitable consequence of life, yet biologists claim that the evidence in favor of such a statement is abundant. Some of the reasons which they urge for this statement is that various single cell organisms, such as protozoa, seem to be in a certain sense immortal, that is, they reproduce themselves by simple division of the body, one individual becoming two, leaving behind them in this process of division nothing which one would recognize as a corpse. And it seems from experimental work that this process can go on indefinitely without any evidence of changes corresponding to senescence and without any rejuvenating process, depending solely upon keeping the environment of the cells favorable. Then, an alluring thought is urged when one considers a germ cell of multicellular organisms in the sense that they are immortal. By this is meant that the germ cell is transmitted from one generation to the next, going on without death, whereas the body cells themselves die. The continuous cycle of propagation of the human family has gone on since the human family first made its appearance among multicellular organisms on the face of the earth.

Then this thought that natural death is a novelty is further borne out in considering certain low organized groups of multicellular animals in which the power of multiplication by budding off a portion of the body, which reproduces a whole, is retained. As long as this asexual mode of reproduction occurs, there is no place for death; in the passage from one generation to the next no residue is left behind. Such a conception of perpetuity in multicellular organisms finds its counterpart in the vegetable kingdom, for example, where the root stock of a perennial plant continues to grow indefinitely. The experiments of Carrel and Delind keeping alive the heart of a chicken embryo for now more than sixteen years, which is longer than the normal life span of a fowl, offers food for reflection. If this can be done in single instances, there seems every reason to believe that by the continuation of such technique the culture can be kept alive indefinitely. Such experiments have been carried out in other highly differentiated cells.

Thus nerve cells, muscle cells, connective tissue cells, epithelial cells, kidney cells, have all been successfully cultivated *in vitro*. It would seem that the foundation has been laid for the statement to be made that there is potential immortality for all essential cellular elements of the body. The question then arises, what causes death among multicellular animals, exclusive of violence. In considering an answer to this query, it might be reasoned that multicellular animals do not share in immortality because of the differentiation and specialization of function of cells and tissues and that in the bulk grouping of these cell tissues of the body as a whole some individual part does not find the conditions necessary for its continued existence. It would seem that it is this very differentiation and specialization of function of a mutually dependent body made up of cell tissue which ultimately results in death rather than to an inherent or inevitable mortal process in an individual cell itself. To quote the thought of one scientist, one reads:

> "When the cells show characteristic senescent changes, it is perhaps because they are reflecting in their morphology and physiology a consequence of their mutually dependent association and not any necessary progressive process inherent in themselves."

In other words, in the light of present knowledge it seems necessary to regard senescence, in part at least, as a phenomena of the multicellular body as a whole, resulting from the fact that it is a differentiated and integrated morphologic and dynamic organization. This phenomenon is reflected morphologically in the component cells, but it apparently does not primarily originate in any particular cell because of the fact that the cell is old in time or because that cell in and of itself has been alive, nor does it occur in the cells when they are removed from the mutually dependent relationship of the organized body as a whole and given appropriate physico-chemical conditions. In short, senescence appears in the present state of knowledge not to be a primary or necessary attribute of the physiological economy of individual cells as such, but rather of the body as a whole.

THE BREAKDOWN CYCLE OF DIFFERENT ORGANS OR SYSTEMS IN THE HUMAN BODY

In pursuing this thought to its logical conclusion, one must become impressed with the difference in time which seems to be characteristic with reference to the breaking point of different organs and systems of the human body. A part of this difference, of course, can be explained on the basis of exposure, a part of it to environmental stress and strain, but there still remains a wide zone which seems to have nothing to explain the time element of breakdown other than that it is just an inherent condition of the structures themselves. An interesting study would come out of this if one looks at the mortality returns in the registration areas of the United States.

TABLE I

Deaths due to organic breakdown or failure of organic systems	Mean age at death (years) Male	Female
1. Alimentary Tract and associated organs of digestion	25	28
2. Respiratory System	32	32
3. Skeletal and Muscular Systems	35	37
4. Endocrinous System	44	44
5. Skin	46	42
6. Reproductive System	47	42
7. Nervous System	49	51
8. Circulatory System, including blood	54	54
9. Excretory System, (kidney and associated structures)	57	54

Considering the figures in this table one is impressed with the differences in time of senescence and ultimate death of different organs or systems in the body. Death in the alimentary tract and associated organs of digestion occurring at an average of 25-28 years as compared with a kidney death at a bit more than 57 years can be explained on no other basis. Of course, environment, that is, external environment, is playing a tremendous *rôle*. In the deaths from the digestive system and respiratory system it must be remembered

that these two systems are constantly in contact with external agencies, such as food and air, while at the bottom of our list the circulatory and the excretory systems do not come in such direct contact.

One may conclude this phase of our consideration of death with the statement that many theories of senescence have been advanced. No one can be regarded as entirely satisfactory. Most of them have the logical defect of setting up some particularly observed atrophy or element of the phenomena of senescence itself, such as the slowing rate of metabolism or protoplasmic hysteresis, offering these as an explanation as to the cause of the whole. Since the question is not yet settled, experimental work must continue, particularly in the direction of producing at will or keeping under control at will the phenomenon of senility without retardation.

THE ETHNOLOGY OF DEATH

The savage of all times and all lands fails to understand death as a natural phenomenon. To him it is inexplicable as a result from natural causes. When he dies without being wounded he is thought to have been the victim of evil spirits with which he has consorted. In Africa the death of a person is usually ascribed to a magician, particularly the magicians of some hostile tribe, or to the malicious act of a neighbor, and this thought has been transplanted with the bringing of the institution of slavery into our country. It is surprising, even at this late date, the tremendous influence which the superstitions of the African negro have had upon the thought of the American people, particularly, of course, those of the South. The peasantry of many countries believe now that disease is the work of demons and in several of them, for example in Australia, death, no matter how evident it may have been the result of natural causes, is usually set down as due to witchcraftry. Among such peoples sleep and trances are regarded as temporary absence of the soul; death is regarded as the permanent absence of the soul, the soul being regarded, so far as they think of it, as the vital principle of the body. This vital principle may be diffused throughout the body according to the thought of some peoples, whereas in others it is believed to be concentrated in one organ. This has given rise to such sports as head-hunting. The term may be personified, as for example, it is sometimes spoken of as the destroyer of life. Conventionally, Death is usually represented as a skeleton with a scythe. An example of the personification of the term occurs in one of Young's lines, which reads:

"Death! Great proprietor of all."

Then the term is also used figuratively, meaning to the last extremity, or utterly, or beyond endurance, as "sick of death" or "tired to death" or to "laugh oneself to death."

DEFINITION OF DEATH

The definition commonly given to death is that it means a cessation of all vital functions without capability of resuscitation. Or again, it may be defined as the permanent cessation of the vital functions of the body. The word as we use it today is the English representative of a similar word common to the Teutonic languages. It means that the ultimate origin of the word comes from the pre-Teutonic verbal stem, "dau." The Swedish and Danish language has the word dead; the Dutch dood; the German dod. There are several synonyms more or less commonly used; deceased is the legal term in ordinary use, thought to be slightly euphonistic or, at least, rhetorical. "Demise" originally was the term used in referring to the death of royalty or some other illustrious personage. It later came into common usage and might be described as a somewhat grandiloquent term for death. Church persons and particularly members of certain religious organizations seem to prefer the words "passed on."

KINDS OF DEATH

(A) Molecular death means the death of a part of the body of a local nature, such as dental caries or necrosis or gangrene.

(B) Somatic death, which means the death of the entire body.

Then one must also make a division of the occurrence of death with reference to the time element if a sane study of the causes is to be made. (a) Chronic causes, or slow causes of death, which connote any continued disease such as tuberculosis or Bright's disease or heart disease of a chronic organic character. These chronic diseases produce relatively slow degenerative changes which after a time, sometimes because of their sum total of alterations from normal, result in the cessation of life. (b) Sudden causes of death. It is under this heading, I think, that the majority of errors are made in listing causes of death; errors because of inability to secure consent of the family for autopsy study, or because of a willingness to save the family from the distress of having an official inquiry into the cause of death, or a willingness to assume responsibility and merely guess at the cause; and, finally, because of a sincere belief that the cause of death is known, though really ignorant as to the actual condition.

THE INTERNATIONAL LIST OF CAUSES OF DEATH

The Bureau of the Census of the Department of Commerce and Labor of the United States Government has issued a list of causes of death known as the International List. It is urged on physicians that the nomenclature adopted by this list be followed in making out their vital statistics returns. There is some argument in favor of the widespread use of such a list in that it does tend a bit more toward scientific accuracy and also does, by virtue of conformity, increase the value of vital statistical returns.

This list sets down more than 250 conditions and diseases as acceptable terms with which to explain death. It might be asked if the list is not unduly lengthy. Yet its inadequacy is admitted when at the end of a section one reads, "Other Diseases." Likewise, one finds the injunction, "never report mere names of symptoms"; it objects to the term "uremia," but accepts "diarrhea"; it agrees to "lack of care" but turns thumbs down on "asthenia"; it says "no" to "ascites" but thinks "chyluria" is splendidly descriptive. "Congestive heart failure" is thought just too utterly provincial, but it nods approval to "pulmonary emphysema"; "surgical shock" just won't do but death by "lightning" is entirely enlightening; "pulmonary hemorrhage" is frowned on, but "uterine hemorrhage, nonpuerperal" is awarded a smile; "homicide by fire-

arms" is no more descriptive than "laparotomy by the surgeon"; why "Pott's disease" is any more descriptive than "white swelling" can only be guessed.

The List is much in need of revision, even remaking. With no thought of offering a classification of the causes of death to replace the International List, but rather for the purpose of simplifying the subject in order that some discussion of the modes of death may be had, the following would seem to meet the requirements:

CAUSES OF DEATH

1. Hemorrhage	8. Hormone Loss
2. Asphyxiation	9. Degenerative Changes in Vital Organs
3. Shock	10. Vascular Changes in Vital Organs
4. Starvation	11. Mechanical
5. Cerebral Anoxemia	12. Congenital Malformations and Anomalies
6. Exhaustion	
7. Paralysis	

This list may not appear adequate, but it surely covers the problem as thoroughly as any I have seen and, at least, has the merit of being original. It would appear useful to inquire into the mechanism of these general causes of death.

(1) *Hemorrhage.* This heading would also include the rupture of aneurysms. Obviously, the size of the vessel involved will determine death or survival of the individual. The larger the vessel the more inevitable the result.

The total volume of blood is from 5 to 7 per cent of the weight of the body. 40 to 50 per cent of this volume is composed of corpuscles. One of the intermediate effects of hemorrhage is fall in blood pressure. The loss of 5 c.c. of blood per kilogram of body weight does not influence pressure; the loss of the next and each succeeding 5 c.c. reduces the pressure about 6 mm. Hg. When a pressure of 50 is recorded the danger limit has been reached; a pressure of 30 makes recovery uncertain, and now symptoms of shock supervene. A loss of 3 per cent or less of body weight from hemorrhage should permit of recovery.

A second effect of hemorrhage is an increase in the pH of the blood plasma. This is followed by a third effect, viz., a reduction of the store of alkaline reserve. Hemolysis occurs, the consequence of dilution of the blood, the plasma becoming definitely reddened. And finally, the loss of the red corpuscles with their cargo results in anoxemia.

(2) *Asphyxiation* may bring about death by interference with the replacement of alveolar air or by the continued inhalation of air poor in required constituents. The first may result from failure of the chest wall to keep in action, as in convulsions, or from a mechanical obstruction, as a foreign body in the larynx. Water may act as such a foreign body, but it should be remembered that one may die after falling in water by shock, concussion, heart failure, hemorrhage or violence. The spasmodic contractions of skeletal muscles commonly preceding death from asphyxia result from the increased excitability of the reflex centers of the cord. The heart slows partly because of hydrogen-ion concentration in the blood and partly because of increased intracranial pressure. Oxygen deprivation excites the vaso-motor constrictor centers, blood pressure promptly rises and hyperpnea results. When the CO_2 percentage of respired air rises to 6 and the O percentage falls to 13.5 it becomes unbearable. A lowering of the alkaline reserve of the blood, reduction of CO_2 tension and hyperpnea all result from a deficiency of oxygen supply. The resulting stimulation of the respiratory center causes a blowing off of CO_2 from the blood into the alveolar air. The pH of the blood is lessened and alkalosis is established. Increased respiratory effort will not relieve the asphyxia because the hemoglobin holds the O with great avidity. If damage to pulmonary epithelium occurs slowly O hunger may not cause respiratory center activity and then the clinical picture of a livid cyanosis wdithout hyperpnoea is seen.

(3) *Shock may kill.* It is the result of many causes. It presents the phenomena of a varying degree of paralysis of the sensory and motor portions of the reflex arc, profound disturbance of the circulatory and respiratory systems and a subnormal temperature. In attempting to classify shock it would appear reasonable to include (a) *gravity* shock, which is the result of stagnation of the blood in the splanchnic vessels. The nerve centers in the brain and cord are rendered anemic. In man the upright posture does not cause gravity shock because of the valves in veins and the *vis a tergo.* (b) *Hemorrhage* shock results in an inadequate filling of the heart with blood during diastole. The effects of hemorrhage have been described. (c) *Anesthesia* shock may be either a primary or secondary condition. The condition seen in the earlier stages of a badly given anesthetic resulting in paralysis of the heart or respiratory center is not shock. A case that has recovered from primary shock, the result of an accident, may have a secondary shock brought about by an anesthetic. (4) *Spinal* shock may result from section of the cord and presents no difficulty in identification by virtue of its local character. (5) *Toxic* shock is best illustrated by the phenomenon known as anaphylaxis. It may result from septic processes through absorption. The shock resulting from intestinal obstruction is now known to be due to absorption of a proteose from the obstructed loops. (6) *Nervous* shock is best demonstrated by the "shell" shocked soldiers in the Great War. Many of these developed the condition after leaving the front. (7) *Surgical* shock is the variety most commonly present when shock is referred to without qualification. It results from accidents, extensive manipulation and especially when there has been extensive muscular destruction. The clinical picture resembles cholera very closely and is a rather common clinical picture.

While the classification just given is a working one, it must be borne in mind that the clinical condition of shock is usually the result of a combination of several factors—hemorrhage, toxins, anesthesia and mental reactions.

(4) *Starvation* may cause death either because of a general failure of all the cells in their functions or because of injury of certain organs that are essential for maintenance of life. That the latter is the more likely factor is evidenced somewhat by the fact that during starvation the loss of protein from the body as a whole rarely amounts to more than 50 per cent at the time of death and it would seem unlikely that general failure of cell function could be the cause. If

it were, death would always occur when a certain fixed loss of protein had occurred.

Certain organs evidently cease to function either because they are deprived of raw material for the elaboration of some substance, such as a *hormone*, which is necessary for life, or because they wear themselves out from sheer lack of nourishment. Starvation usually ends in death in the adult in something over thirty days; it is very much sooner in children because of their more active metabolism. The total loss of body weight at the time of death from starvation may be as much as 50 per cent of the original. The body temperature does not change greatly until within a few days of death, when it begins to fall. The blood sugar drops rather rapidly early in the starvation period, but after it reaches a varying level it remains fairly steady thereafter. This is explained by the fact that practically all available glycogen has been used up after the first three or four days of starvation. The available glycogen thereafter is derived from the proteins and fat of the body of the person being starved. Even the glycogen content of the skeletal muscles is reduced. The condition of acidosis supervenes. The acids responsible for the condition are derived from the incomplete combustion of fat. This may amount to as much as 10 or 15 grams per day, particularly in obese individuals. During the greater part of the starvation period most of the energy required to maintain life is of fat derivation. When the available supply has become exhausted, then protein metabolism sets in at an increased rate and as a consequence the nitrogen secretion rises. When this occurs it may be considered as a harbinger of death and is sometimes spoken of as the "ante-mortem rise in nitrogen excretions." It really means that all of the fuel of the animal economy has been used up, or in other words, that the working capital has been exhausted.

(5) *Cerebral anoxemia.* The physiological integrity of the cerebrum is an essential factor in the preservation of consciousness. The exact nature of this state of awareness is not known, but a number of factors on which it depends are known. One of these is the maintenance of the blood supply. Whatever raises the cranial cavity pressure above that of the cerebral veins and capillaries causes obstruction to cerebral circulation in varying degrees to the absolute. Tumor, abscess or hemorrhage, by pressure, produces symptoms first of cerebral structures, but is prevented from pressing on medullary vessels by the falx cerebri and cerebelli. But as the brain stem is pressed downward the medulla is pressed against the foramen magnum and failure of respiration or circulation or both ends the drama. Also general circulatory conditions affecting the amount of carotid blood supply will affect consciousness. Prior to anaesthesia days, pressure on the carotids was resorted to for the induction of unconsciousness. When the vasomotor tone of the abdomen is lost, most of the body blood can gravitate there, and unconsciousness results. Even the pooling of blood in the skin vessels, as when taking a hot bath, may cause syncope. Removal of fluid in pleurisy or in ascites may, if done rapidly or too completely, cause syncope. Carried beyond certain limitations, any of these conditions may cause death.

By anoxemia one intends to mean a tissue oxygen want instead of respiratory inadequacy. It is distinct from carbon dioxide retention, though it may be coincident with it. An anoxemia may obtain with a normal CO_2 in the blood. Of it Haldane wrote, "It not only stops the machine, it wrecks the machinery." By forced breathing one may induce a respiratory center anoxemia in which condition there is no carbon dioxide retention. Another illustration is found in carbon monoxide poisoning, in which condition the hemoglobin is saturated with the gas to the exclusion of oxygen, hence anoxemia. It is anoxemia that limits man in search of new altitudes. Carbon dioxide is below normal in lobar pneumonia because of anoxemia, which causes hyperpnea, and this in turn washes the carbon dioxide out of the blood.

A reduction of carbon dioxide in the blood not only withdraws the physiological stimulus to the respiratory center, but hinders the dissociation of oxygen from hemoglobin. While all tissues present evidences of oxygen hunger, those of the nervous system have been demonstrated to be peculiarly sensitive. Barcroft classified anoxemia into (a) anoxic, (b) anemic and (c) stagnant. Such a grouping merely means that there may be an inadequate oxygen absorption from the lung, a blood under-laden with oxygen or a poor delivery of a blood normally loaded. They all imply oxygen debt and when the physiological adaptation of the circulatory apparatus cannot fit itself to the situation, distress even to the extent of death may supervene.

The syndrome of anoxemia must of necessity be either local or general. A disturbed digestion, for example, may result from a poor gastric circulation; an embolus blocks a vessel and an area of tissue is deprived of blood supply, with pain, edema and necrosis resulting. When the central nervous system is involved, restlessness, irritability, delirium, coma, death follow in slow or rapid succession as determined by the degree of oxygen want.

(6) *Exhaustion* may constitute a mechanism of death, the result of numerous agencies. But the conception should be limited to those agencies which, directly or indirectly, induce a state of exhaustion of cellular structure. Exhaustion derives from *exhaurire*, a term conveying the thought of "using up, to empty." While sharing some features in common with starvation and paralysis, it would seem to rank a special place in the causes of death. Some agents may cause this by the circuitous route of over stimulation; strychnine, primarily, activates the cells of the spinal centers, the medullary centers being indifferently involved. The drug is even more selective in its action, the primary stimulating or convulsant effect being confined to the sensory, not the motor cells of the cord. It is true that asphyxiation may become a part of the picture in death from strychnine, but it in turn is a result of exhaustion of the respiratory centers from over activity. While death may occur in strychnine poisoning because of respiratory spasm during the convulsant period, the usual cause is exhaustion of the spinal cord, medulla and sometimes the cardiac muscle.

A number of other poisons belong to this *convulsant* group. The picrotoxin group and the caffein group are ready examples.

(7) *Paralysis* might be defined in this discussion, in which the term is given a place in the causes of death, as a loss of function by direct depression. Some poisons produce death with no intervening stimulating period; a stage of irritability may supervene, but not

true stimulation. In this group will be found the toxins of such organisms as tetanus bacillus, the bacillus of diphtheria. such poisons as snake venom, alcohol, some anesthetics, many of the agents in the hypnotic and narcotic groups and such disease entities as progressive bulbar paralysis and acute ascending paralysis. When the effects of such agents are confined to non vital organs only local paralysis ensues. Death results when vital organs are attacked.

(8) Some of the *endocrine group* are essential to vital processes. A kind of vegetative existence can be maintained without thyroid function; life is not dependent upon gland activity. But some of the group are essential, e.g., the pituitary, the parathyroid and the adrenals. The problem of hormone loss is made complicated by the interrelationship in function. But such dependency strengthens rather than weakens the thesis of death from essential hormone loss. Whatever causes may establish this hormone loss are, of course, thus indirectly responsible for the death.

The next heading, Degenerative Changes of Vital Organs, might thus be conceived to remove the necessity for the listing of hormone loss as a cause, but not all of the diseases of these glands are degenerative. It may be acknowledged at once that many of the causes here considered necessarily overlap.

(9) *Degenerative Changes in Vital Organs:* Degenerative changes, when complete, cause death of any organ or cell. As stated under another heading, when local there is local death, and when vital organs are subjected to such processes death of the whole body occurs. If one embraces in a definition of the term degeneration a conception of a retrogressive pathological change in cells or tissues, in consequence of which the functioning power is lost and the living substance becomes converted into an inert mass, then may one appreciate the importance of this heading as a cause of death.

Then, too, if one pursues the subject a bit further and takes cognigence of the many kinds of degenerative changes a cell or tissue may undergo, it must be apparent that degenerative changes of vital organs bulk large as causes of death. Of these kinds, fatty, amyloid, angiolithic, hyaline, cystic, Wallerian, come readily to mind.

It is of importance to remember that degenerative changes in a peripheral nerve may be repaired by regeneration, whereas destruction of fibers in the central nervous system results in a permanent damage or death.

(10) *Vascular Changes in Vital Organs.* It requires no effort to establish complete obstruction of one of the main coronary arteries as a cause of death. Such a disaster may result from a thrombus, an embolus or obliteration of the lumen by multiplication of mural tissue.

That a spasm of vessel walls may cause death by local anemia is more equivocal. Yet experiments have demonstrated that complete anemia cannot be survived after a rather fixed period of time—a period which varies with different cell structures. Cerebral cells cannot be restored after eight minutes of anemia, medullary cells thirty minutes, while myenteric cells may live after seven hours. Such susceptibility helps explain why consciousness is lost early after circulatory failure of the brain. It also helps one to understand why such a faithful relationship obtains between the nutritional demands of a structure and its vascular distribution. The grey matter of the medulla has a richer capillary network than has that of the cord. Sensory neurons are in an almost constant state of activity, while the motor neurons exhibit a more intermittent activity; hence one is not surprised to find the former more richly vascularized than the latter.

(11) *Mechanical Causes.* But little space need be devoted to this section. The relationship between cause and effect is sufficiently apparent where grosser injuries are involved. Here the trauma is sufficiently massive that when vital structures are wrecked there is small need for invoking shock, hemorrhage and other fundamental causes as contributing factors. A piece of metal driven through the medulla kills by virtue of physical destruction; a similar damage of the nodal tissue around the mouths of the great veins in the right auricle kills at once. Birth trauma accounts for 34 per cent of deaths in the newborn and it is of interest to note that of this group of birth traumas 81 per cent was due to a tear of the tentorium cerebelli.

(12) Finally, 5 per cent of deaths of the newborn are due to *congenital malformations and anomalies.* Many of these are self explanatory and inconsistent with life, especially involving the central nervous system and the heart. Anacephalus, meningocele, hydrocephalus internus, stenosis of the conus pulmonalis, transposition of large vessels, a three-chambered heart, eventration, are a few of the more common; and the list is not exhausted.

DEATH RATE

Death rate is a term that arbitrarily expresses the mortality of a place based on the number of deaths for each one thousand of its population during a period of one year. To determine the death rate of a given place, multiply the number of deaths by 1,000 and divide the product by the population. So many factors influence the death rate of any community that a single yearly study of states or cities affords little real insight into the actual statistical death rate. To be worthwhile such a comparison must be made over a period of several years, say ten, hence it is obvious that the comparison of death rates of different communities for a short period may be markedly modified by the presence or absence of an epidemic of some acute transmissible disease, which might run a death rate for a given short period up 20 or 30 or 40 per cent higher than the average death rate when considered over a long period of time. For example, one might take the death rate of Seattle, Washington, for the year 1913, when it was 8.4, and compare that rate with the rate of Richmond, Virginia, which in the same year was 20.4. Certainly no such disparaging health ratios exist between the latter and the former city if studied over longer periods.

Likewise, the incidence of mortality is not equally distributed over all age periods. The rate is highest at the two extremes of the life span. A population with a high birth rate or one with a high average life span would have a high death rate when all ages and both sexes were considered only as components of the group. This form of determination is called *crude death rate* and must be reckoned as an unsound basis

for comparison of relative mortality of one country with another.

For such comparisons what is known as a *standardized death rate* should be used. To obtain such rates it must be found what the death rate would have been if the population had been made up as to sex and age on a fixed basis. Even this method is subject to objections, for such rates must vary according to the standard adopted. Therefore, the only accurate method is to use rates based on figures obtained from studies for different sex and age groups. The factor of sex must be included, since in most countries the death rate of males is higher than in females. There being more widows than widowers explains the remarkable fact that more than fifty per cent of the wealth of this country is in the hands of women.

A comparison of the death rate for various countries is given in Table II. It is necessary to make clear that these comparisons are drawn on a *crude death rate* basis, as explained above.

TABLE II

Comparison of Death Rate in Different Countries

	Years			
Country	1876	1901	1913	1926
England	20.9	16.9	13.8	11.6
France	22.6	20.1	17.7	17.5
Germany	26.3	20.7	15.0	11.9
Italy	28.8	22.0	18.7	16.8
Netherlands	23.5	17.2	12.4	9.8
Sweden	19.6	16.1	13.6	11.8
Switzerland	24.3	18.0	14.3	11.7
Australia	17.6	12.2	10.8	9.4
New Zealand	11.8	9.8	9.5	8.7
Japan		20.4		21.2

These tables indicate a definite decline in all the countries except Japan. The least improvement is shown by Germany and Italy. In some the rate has fallen as much as 50 per cent. This decline has not been spread over the whole life span. Since 1876 it was 65 per cent under five years of age and only 32 for 70 to 80 years in England, while in the U. S. it has been 40 per cent in 44 years. In New Zealand the decline has been but 26 per cent, which must be interpreted in the light of the lowest rate at the beginning of the period studied of any nation in the group. It would appear that New Zealand's figures might be accepted as an expression of the existence of an irreducible minimum.

Figures for the U. S. covering these periods are not available to the writer at present, but the nearest comparable rates are given in Table III.

TABLE III

Death Rates for U. S. in Each Decennial Census Period

Census Period	Rate
1880	19.8
1900	17.6
1910	15.0
1920	16.2
1930	11.8

THE TERM IN MEDICAL JURISPRUDENCE

The law divides death into two kinds, natural death and civil death. Natural death is defined as "cessation of life." The law considers a natural death as one which occurs by the unassisted operation of natural causes as distinguished from what is known legally as a "violent death," which is defined as one caused or accelerated by the interference of some human agency. The law defines "civil death" as the state of a person who, though possessing natural life, has lost all his civil rights and, as to them, is considered dead. Thus, a person attained and convicted of felony and sent to State prison for life, in consequence of conviction and sentence, is considered as civilly dead. This doctrine was handed down from the common law of England. Then the law makes some distinction between the term "real death" and "apparent death" and says that real death is distinguished by the absence of heart beat and respiration.

The law also sets up certain signs or indications by which it can admit that death has occurred. For instance, (1) when the body is the temperature of the surrounding air; (2) intermittent shocks of electricity of different tensions give no indication of muscular irritability; (3) movements of the joints of the extremities and of the jaw showing more or less rigor mortis; (4) a bright needle plunged into the biceps and left there shows no sign of oxidation on withdrawal; (5) the opening of a vein shows the blood has coagulated; (6) the subcutaneous injection of ammonia causes a dirty brown stain; (7) a filet applied to the arm causes no swelling of the veins on the distal side; (8) after death there is an absence of the translucency when the hand is held before a strong light with the fingers extended but not in contact; (9) after death there is a loss of pupillary reaction to light and to mydriatics, as well as a loss of corneal translucency.

THE LEGAL CONSEQUENCES OF DEATH

The burden of proof rests with the party who asserts that a person is dead. In other words, the law presumes that a person who is once shown to have been in life is presumed thus continued until the contrary is shown. The law does not even accept the record of probation of a will as competent evidence of death of the man who wrote the will. Out of the French civil code grew the attempts to determine the question of survivorship when several persons perish together as the result of the same event, such as a shipwreck or a battle or an accident, etc. Strength, age and difference of sex of the parties dying together constitute the factors around which the attempt is made to make such differentiation. For example, if of those dying one was under fifteen and another was thirty, the eldest was presumed to be the survivor. If all were over sixty, but one only sixty-one, that one was presumed to be the survivor. If all were presumably the same age, the male was presumed to be the survivor. The civil code of Louisiana laid down such rules, but the rest of the states of this country, which have derived much of their law from English common law, have never adopted these provisions and require that survivorship of two or more shall be proved by facts, not by any settled legal rule or prescribed presumption.

As to contracts in general are not affected by death of either party. The executors or administrators of the deceased are required and expected to fulfill all of his engagements and may enforce all of those in his favor.

While this statement is made as a general rule, of course there are exceptions, as for example, the contract of marriage necessarily must be terminated by the death of one of the parties. Likewise, a contract for partnership.

Something of the same rule applies with reference to crimes. If a person who is accused of a crime dies before trial, no procedure can be had against his representatives or his estate or heirs.

As to inheritance when a person possessed of real estate or personal property dies after having made a will, his real and personal property after satisfaction of his debts is to be distributed as directed in his will. But if one dies intestate, his real estate goes to his heirs as a law under the Statute of Descent of that state, while his personal property goes to the administrators to be distributed to the next of kin under the Statute of Distribution of that state.

The term "dead-born" means that a child born dead is to be considered as if it had never been conceived or born. In other words, it is presumed that it never had life, as it is a maxim of the common law that *mortuus exitus non-exitus*. It is also a doctrine of the civil law that not to be born and to be born dead are equivalent terms; the Latin is *non nasci et natum mori*.

DEAD BODY

The law defines a dead body as a corpse and sets up the dictum that there is no right of property in the ordinary sense of the word in a dead human body. There are, however, certain rights attached to it which the law protects and for the health and protection of society it is a rule of the common law, and has been confirmed by statute in many states, that public duties are imposed on public officers and private duties upon husband or wife or next of kin of the deceased, to protect the body from violation and see that it is properly buried and protected after burial. The executors, for example, have a right to possession of the dead body to preserve it for burial. The right to make testamentary directions as to the disposal of the dead body has been conferred by statute in a number of states. It has generally been decided that in the absence of testamentary disposition, the right and duty of burial devolves upon the relatives in the following order as named,—(1) husband or wife, (2) children, (3) father and mother, (4) brothers and sisters, (5) next of kin. The law also holds that the expenses for a funeral are necessary expenses and for which the estate of the deceased is held liable. The leaving unburied of a corpse of a person for whom one is bound to provide Christian burial is an indictable misdemeanor if it can be shown that he had been of ability to provide such burial. Any householder in whose house a dead body lies is bound by the common law, if he has the means to do so, to inter the body. To disinter a dead body without lawful authority, even for the purposes of dissection, is a misdemeanor for which the offender may be indicted under common law. Some of the States of the Union have statutes that make this offense punishable. It is not considered under common law to be larceny to steal a dead body, but if one steal the clothes from that dead body, he then can be charged as guilty of larceny. The right of burial having once been exercised by the person charged with that duty gives him no right to the corpse except to protect it from unlawful interference. Autopsy may be made by a physician under legal direction and at the request of the crime has been committed and he does not render himself liable by removing, for instance, a portion of the skull under the direction of the coroner.

It is the coroner's duty after death by violence to cause an autopsy to be made. The physician who makes it can recover from the local government for his labor. The matter of ordering autopsies and the dissections of dead bodies or exhuming them for that service has been regulated by statute in nearly all the states of this country. The preventing a dead body from being interred is an indictable offense in most states. The purchaser of land upon which is located a burial ground may be enjoined from moving bodies therefrom if he attempts to do so against the wishes of relatives or next of kin of the deceased. Every burial is a concession of the privilege that cannot afterward be repealed and the purchaser's title to the ground is fettered with the right of burial. However, the right of a municipal or state authority, with the consent of the owner of the burial lot or in execution of eminent domain, to remove dead bodies from cemeteries is a well settled fact in law. Neither can one seize a dead body on the pretense of arresting it for debt, and such seizure is considered *contra bonus mores* and an extortion on the relatives. Some states provide by statute that such an act is a misdemeanor. A widow who permits her husband to be buried in a certain place may not disturb his remains, her right to the body of her deceased husband being terminated by the burial and any further disposition of such body belonging thereafter exclusively to his next of kin.

THE TERM IN THEOLOGY

Here it is intended to mean the cessation of spiritual life and therefore comes to be called spiritual death. Such a conception is an essential part of particularly the Christian and Jewish religious. By inference spiritual death may be conceived of as an alienation from God or as an annihilation of the spirit in consequence of sin, as for example, in Romans 8:6 one reads, "To be carnally minded is death."

SECTION XII—"*The Clinic*"

"Milk of Calcium Bile"-- A Report of Two Instances*

By

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and

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THE finding of "milk of calcium" in the gall bladder as a cause for abdominal symptoms is sufficiently frequent to warrant the report of cases as discovered. We, therefore, offer a discussion of the following two cases for consideration and stimulation. Both were correctly diagnosed pre-operatively by cholecystography:

Case I. F. K., White, Female, Housewife, age 34 years. Since the birth of a child 10 years prior to date, she complained of recurrent attacks of sharp pain in the right hypochondrium, radiating to the right sub-scapular area. Each attack was accompanied by nausea and vomiting, lasting several hours and frequently relieved by heat. There was no relationship to food intake. Attacks have come on more frequently in the last few years. There had been no jaundice.

On examination, there was marked tenderness in the gall bladder region and a suggestive palpable mass. Cholecystography revealed several calcified shadows in this region, one somewhat irregular, identified as a stone in the cystic duct, the other changing its appearance at different times and at different angles. There was no filling of the gall bladder after the oral administration of the dye.

Operation: A subacutely inflamed thick walled gall bladder was found and removed. On palpation it appeared to contain a sandy substance with a definite stone in the cystic duct as seen on the X-ray film. There were no adhesions, no calculi in the common duct. The appendix, likewise, was removed.

Pathological description: "The external surface of the gall bladder found smooth and glistening, the mucosal surface is trabeculated. The lumen contained 15 c.c. of colorless mucinous fluid and approximately 5 c.c. of a chalky white material having the consistency of "cottage cheese." The lumen of the duct is occluded by a white coral-like concretion. No chemical examination of the contents was made."

Diagnosis: "Milk of calcium bile"; sub-acute cholecystitis; cystic duct block by calculus.

Case II. This case is reported through the courtesy of Dr. M. J. Matzner of our department.

T. F., Female, Housewife, age 52 years.

Fourteen days prior to admission, patient had an attack of generalized abdominal cramps, localizing in the right upper quadrant with radiation to the right lower back. This pain was accompanied by nausea, no vomiting. Six days later, and again the night before admission, patient experienced similar attacks. There had been no jaundice at any time.

Physical examination: Revealed moderate tenderness in the right upper quadrant with no palpable mass.

Laboratory findings: Urine: showed the presence of bile and ½% of sugar. Blood: 15,000 RBC and a poly count of 89. Blood count showed a slight anemia; icteric index was normal; bilirubin showed a direct immediate positive and an indirect of 8 units. Blood chemistry: showed a somewhat low urea and high uric acid.

X-ray examination: showed a calcified semi-lunar shadow in the gall bladder region, several small calcareous shadows likewise seen above that. At a later period, after the administration of the dye, there was no increase of this shadow except for a diffusion of shadow on several of the films.

Operative findings: The gall bladder was adherent to the omentum; was distended; its walls opaque and thickened; did not empty readily. Cholecystectomy was performed.

Pathologic description: "The gall bladder had a red, granular, serous surface with markedly thickened walls; the mucosa was hemorrhagic and covered with small amount of inspissated, clay-like material with an occasional small stone of soft consistency.

DISCUSSION

That calcific deposition within the gall bladder either of stones or as so-called gravel or as "milk of calcium," as found in these two cases, can be productive of symptoms, has been known for years. It seems superfluous to review the previous reports by other observers. The article by Kornblum and Hall in the American Journal of Roentgenology in May, 1935, covers these very thoroughly. However the importance of this contribution is in the discussion and study of the X-ray findings. A semi-lunar, calcified shadow in the gall bladder region which is present on the control or zero hour film and persistent at all times, should

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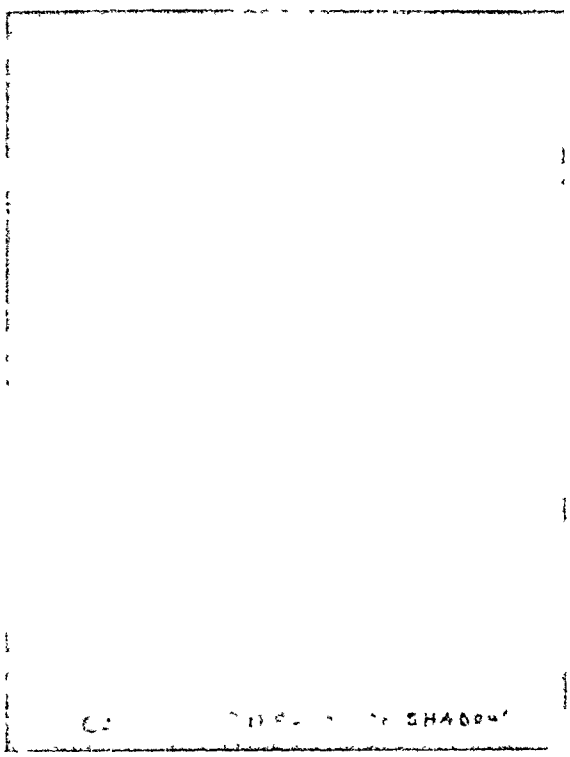


Fig. 1

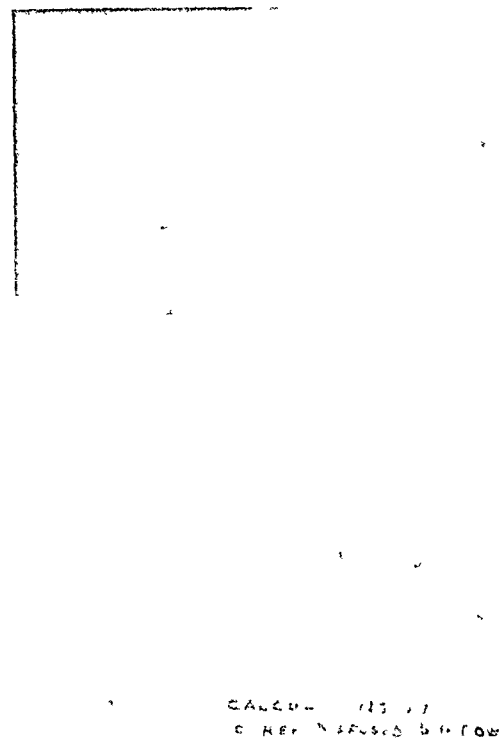


Fig. 3

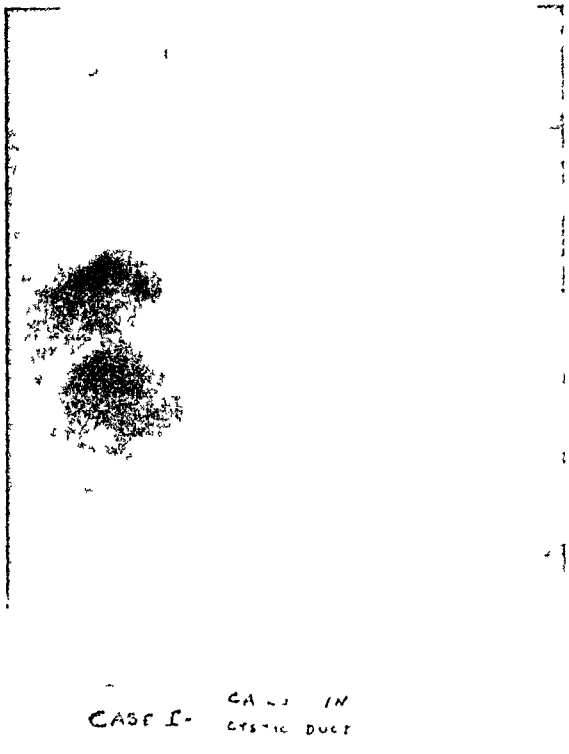


Fig. 2

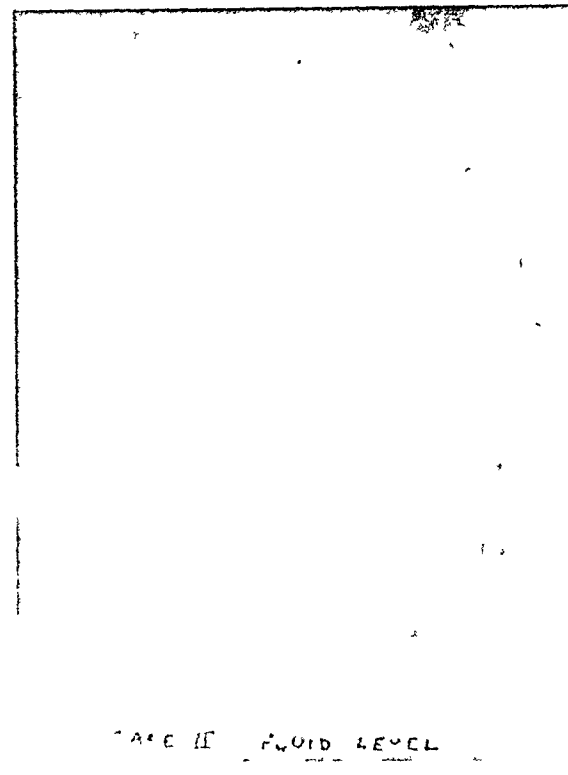


Fig. 4

make one suspicious of this "milk of calcium bile." If this shadow diffuses or changes its appearance, in spite of its persistence, one should be doubly aware of such a diagnosis. The finding of a fluid level with a horizontal line is of great significance. The further finding of stones in the cystic duct is likewise of extreme importance.

We therefore add these two cases to the medical literature because: 1. these cases are not infrequent. 2. they produce interesting X-ray shadows. 3. they emphasize the importance of the relationship between the deposit of calcium in the bile and the production of gall stones.

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ABSTRACTS

CLINICAL MEDICINE

WILLETT, JOSEPH C., SIGOLOFF, EMANUEL, AND PFAU, CLIFFORD L.

An Institutional Outbreak of Epidemic Jaundice. J. A. M. A., Vol. 106, pp. 1644-1646, May 9, 1936.

An outbreak of jaundice occurring in a novitiate in St. Louis County during October, 1934, was investigated. Of 132 male students, 32 developed the disease. In the majority of cases it was relatively mild, characterized by a slight, initial elevation of temperature, nausea, vomiting, anorexia, abdominal pain, clay colored stools, bile stained urine and jaundice which in most cases varied from a slight yellowish brown to a deep brown tint. In most cases the jaundice appeared between the first and the fourth day, but in four cases it appeared on the seventh and eighth days. In some of the cases the spleen was palpable, while in others it was not.

The clinical picture suggested Weil's disease. To establish this the demonstration of the Leptospera icterohemorrhagiae was attempted. All material from the patient did not reveal the presence of the Leptospera either upon darkfield examination or guinea pig inoculation. Specimens of water from the holy water fonts revealed organisms identical in morphology and motility with the Leptospera, but guinea pig inoculation produced no infection. However, after the sanitary condition of the fonts was improved the epidemic subsided.

Francis D. Murphy, Milwaukee.

BASSLER, ANTHONY.

Intestinal Obstruction Due to Amebiasis. J. A. M. A., June 6, 1936, Vol. 106, pp. 1960-1968.

A man, aged 50, was first seen by a doctor because of abdominal cramps. The case was referred to the author. The history revealed a man who had been in Chicago during the epidemic of amebiasis eight weeks prior to the onset of the aforementioned symptoms. A diagnosis of amebic dysentery was made and treatment begun. Throughout the course of the next two years it was necessary to continue the treatment because of repeated flare-ups. Late in the second year he was operated on for acute intestinal obstruction by a Chicago surgeon who found a firm annular mass in the colon. About two weeks after the operation he passed some blood and pus from the rectum. This material was found to be full of amoeba. Five weeks after operation his wound became inflamed and started to slough. Examination of this material also was positive for amoebae.

Roentgenograms made after the operation revealed the strictured section of the descending colon. He was constantly under observation and treatment for amebiasis during this time. Frequent roentgenograms were also made which revealed that the strictured condition was clearing up.

This is probably a case of complete intestinal obstruction due to amebiasis. This is an exceedingly rare occurrence, especially since the obstruction was in the sigmoid and not in the cecum or ascending colon as is usually the case.

Francis D. Murphy, Milwaukee.

HECK, F. J., AND WALTERS, WALTMAN.

Development of Macrocytic Anemia Following Resection of the Stomach. Proceedings of the Staff Meetings of the Mayo Clinic. Vol. 11, No. 8, Feb. 19, 1936.

A case is presented of a woman aged 48, with a preceding history of biliary disease, who before final operation presented achlorhydria after an Ewald meal, plus a simple microcytic anemia, but who a year following gastric resection for extensive but localized carcinoma of the stomach presented a macrocytic anemia which was regarded as pernicious (Addisonian) anemia. The discussion of this case is of interest because comparatively few instances of pernicious anemia following gastrectomy are on record, even where the gastrectomy has been total. In this case it was about two-thirds. Moynihan had some evidence of 4 such instances following total resection and Hurst collected one or two others. The striking fact is that even after total gastrectomy where the patient has survived for a few years pernicious anemia does not as a rule, but only exceptionally occur, and the same is even truer of cases in which partial gastrectomy has been done. In fact after partial gastrectomy anemia of any kind is rare. The achlorhydria shown to exist before the final operation was detected by the ordinary Ewald meal and not by histamine injection, but it is at least probable that an achylia gastrica existed.

If we assume that achylia gastrica existed before the final operation for cancer of the stomach, then the intermediate problem of the possible relationship between the achylia and the cancer would be solved by certain investigators, such as Bloomfield, by saying that the gastritis associated with achylia was the factor of irritation producing the cancer, and Hurst would be of the same opinion. Then to classify the preoperative simple anemia as "the idiopathic type of hypochromic anemia" or the achlorhydric microcytic anemia of women is scarcely more logical than to regard it as one of the types of simple anemia which accompany early cancer of the stomach. Indeed there is also a macrocytic anemia associated with cancer of the stomach closely resembling pernicious anemia in smear picture with even glossitis but which may be differentiated from Addison's anemia by a usually higher white blood cell count and by the absence of bilirubinemia and spinal cord changes. In this case there is no record of pigment studies or of neurological examination, although the low leukocyte count favors Addison's anemia. It seems to the reviewer most probable that this patient had the potential *makings* of a true Addison's anemia: if Walters had not so

ably removed her unsuspected cancer she would have died of cancer without ever having pernicious anemia: the successful removal of the cancer allowed the pernicious anemia to develop and in fact the operation itself may have been the "precipitating factor" in bringing on the pernicious anemia, just as pyelitis or pneumonia or a severe nerve strain often precipitates this disease in those who are on the edge of it all the time. The authors believe that the patient may have had pernicious anemia the time she was first seen and that as a result of continued hemorrhage a hypochromic anemia developed and was superimposed on the Addison's anemia, with a resulting microcytic smear picture. This however is impossible, because if a patient with a fully developed Addison's anemia has to contend with the added factor of blood loss from hemorrhage the resultant smear picture is still decidedly macrocytic and the only difference is a lower color index and some degree of comparative achromia. The superimposition of hemorrhagic upon pernicious anemia never influences the morphology of the erythrocytes. As the reviewer has shown years ago, Addison's anemia may be suddenly engrafted upon a simple anemia or upon a normal blood and as soon as it is so engrafted, we see first a distortion of the erythrocytes toward the macrocytic type and with anisocytosis even before there is any oligocythemia or even hemoglobinemia.

Beaumont S. Cornell, Fort Wayne.

THOMPSON, J. W., AND SOPER, H. W.

Combined Medical and Surgical Management of Peptic Ulcer: with Emphasis on the Treatment of Hemorrhage. Ann. Int. Med., Vol. 9, No. 8, 1936.

This article is worth careful study, not only because of the unusually wide-angled viewpoint of the authors, but also because certain of their contentions seem challenging in spite of their good results. Perhaps if all clinicians were to adopt some one good logical course of procedure in treatment as they have done, their results might be better than where the technique is permitted to vary too widely with different cases. Their use of a smooth diet, with frequent feedings to the practical exclusion of alkali is as sane as their good results indicate, and the routine use of sedative and belladonna cannot be overemphasized. Egg white in the raw state is given with apparent benefit, but it would seem that this may be due to some physical effect for it has long since been demonstrated that raw egg white is not digested in the human being. It is a pleasure to hear authors make a plea for the careful *medical* treatment of gastric ulcer, in spite of the danger of confusion with cancer: today there is too great a tendency to refer all stomach ulcerations at once for surgery, forgetting, as the authors do not forget, that gastric surgery, except in the most expert hands still carries an alarming mortality. Where medical treatment is used it goes without saying that the most careful check must be kept up by X-ray on the progress or otherwise of the lesion. The persistence of occult blood in the stools is one of the danger signals of malignancy and should result in surgery. Soper has been using evaporated milk in ulcer treatment for some time, one of the reasons being its sterility. The use of the transgastric indwelling nasal catheter of Levin, recommended by the authors in resistent cases of gastric ulcer, for the purpose of placing food directly into the jejunum and thereby offering the stomach a much needed rest seems in their hands to work well, but it still seems questionable if the good results are due to gastric rest or to limitation of gastric secretion. For example what evidence is there that regurgitation from the duodenum is not actually increased by this method and that such increased regurgitation is not the cause of the good results by acid neutralization. And again, while these authors have obtained good results in ulcer bleeding by the use of the indwelling gastric catheter, through which thromboplastic agents are introduced and by which blood is aspirated, what proof is forthcoming that the presence of the catheter does not actually by its own presence induce much unusual peristalsis? Here are two problems deserving early experimental study.

Beaumont S. Cornell, Fort Wayne.

BASSLER, ANTHONY.

Intestinal Obstruction Due to Amebiasis. J. A. M. A., Vol. 106, 28, June 6, 1936.

A case of amebiasis, acquired in Chicago during the well known epidemic of 1933, proved extremely resistent to the repeated use of all the approved antiamebic remedies as evidenced by recurring attacks of diarrhea and malaise, and the case progressed to a complete intestinal obstruction with fecal vomiting and required emergency caecostomy. Few reports have previously been made of amebic stenosis occurring in the sigmoid which proved to be the case here. Under the influence of further strenuous treatment with vioform, chiniofon, and emetin, the obstruction at the rectosigmoid juncture has given every evidence of disappearing, although it was the impression of the surgeon who operated that obstruction was due to a carcinoma. The report of this case is of importance because of the unusual position of the amebic obstruction, and indicates the importance of not assuming that all obstructions in this region are malignant and therefore less amenable to treatment.

Beaumont S. Cornell, Fort Wayne.

VINSON, P. P., AND BUTT, HUGH R.

Esophagitis: A Clinical Study. J. A. M. A., Vol. 106, pp. 994-996, March 21, 1936.

Much has been written about carcinoma and stricture of the esophagus, but nothing about the commonest pathological condition here, esophagitis. In a recent study, it was found that of 3,032 autopsies, 213 cases, or 7.02% of cases showed evidence of esophagitis. In 10.3 per cent of these cases, there were definite clinical symptoms.

The condition occurs most frequently when there is severe vomiting, or after the passage of a stomach tube. It is also associated with pyloric or duodenal stenosis, gall bladder disease, and occasionally appendicitis.

The most frequent symptom is a burning pain in the region of the middle and lower third of the esophagus, much like that occurring in peptic ulcer. The next most frequent symptom is hematemesis. Dysphagia and melena also occur in some cases.

The simplest treatment is prevention. Vomiting should be controlled as much as possible. Ethyl aminobenzoate lozenges dissolved in the mouth may relieve some of the pain. A bland, smooth diet should also be used. Tincture of belladonna, 20 drops every three or four hours, may relieve the spasm. When ulceration occurs, the passage of a bougie may stretch the base of the ulcer and bring about complete healing.

Francis D. Murphy, Milwaukee.

GAY, L. P.

Gastro-Intestinal Allergy — the Leukopenic Index as a Method of Specific Diagnosis of Allergens Causing Peptic Ulcer. J. A. M. A., Vol. 106, pp. 969-976, March 21, 1936.

The introduction of the leukopenic index as a method of allergic diagnosis is due to the work of Vaughn. He observed that allergens caused a leukopenia in individuals sensitive to a certain allergen and a rise in the leukocytes in individuals not sensitive to that certain allergen. This type of diagnosis has been used in asthma, allergic headache, hypersensitive rhinitis and gastro-intestinal allergies.

This is the report of the treatment of six unselected ulcer cases treated on the premise that peptic ulcer is an allergic manifestation. In three of the six cases there was an allergic history. It was noticed that wheat and milk were definite allergens in all the cases, and egg in 50 per cent of the cases. In these cases skin tests were of little or no value because the clinical reactions of some of the allergens are of the cumulative type. The use of the leukopenic index is the method which was used in determining the allergens.

It was found that an immediate leukopenia was indicative of an aller-

gen, and a leukopenia of slight degree followed by a hyperleukocytosis was of the same significance. It was also found that those foods which produced a leukopenia produced an achlorhydria, and vice versa.

The conclusion was reached that complete relief of peptic ulcer symptoms by a diet that is compatible with the leukopenic index; that relief of pain with conventional methods was due to a state of antianaphylaxis; and that the pain of peptic ulcer was due to a localized anaphylactic spasm.

Francis D. Murphy, Milwaukee.

WALKER, HARRY.

The Etiology of Abdominal Pain in Diabetic Acidosis. Ann. Int. Med., IX, 1178, March, 1936.

The importance of making a correct differential diagnosis, thus avoiding the danger of emergency surgical operations on patients on the verge of diabetic coma, on the one hand, and the seriousness of a delay too long of an operation in diabetics that demand emergency surgery is stressed in the rather small group of patients in which it is difficult or impossible to determine whether or not there is an intra-abdominal surgical lesion present or whether the symptom complex is one entirely due to acidosis. A case is reported to illustrate the difficulty referred to. A diabetic of two years duration was on a weighed diet and a fixed dosage of 60 units of Insulin daily. For 24 hours preceding admission to a hospital an insufficient amount of Insulin was taken. During the following night nausea and vomiting occurred, with the ingestion of large amounts of water. After midnight the patient experienced a sudden attack of sharp pain in the epigastrium, which increased in severity, soon extending over the entire abdomen and radiating to the chest as high as the suprasternal notch. The pain was increased by deep inspiration. The nausea and vomiting, together with the pain, continued, all increasing in severity. During the night an additional 40 units of Insulin was given without any appreciable effect either on the vomiting or the pain. On admission to the hospital the following afternoon a blood sugar of 444 was found, with a plasma CO_2 combining power of 20.2 volumes per cent. With the administration of 50 units of Insulin hypodermically and 1000 c.c. of normal saline by the vein the abdominal pain disappeared completely in three-quarters of an hour and the abdomen became soft.

Attention is called to the infrequency of reports of similar cases, but the observations of McKittrick are quoted. These are (1) Patients that have been studied with operations and no surgical lesion found suggested before the operation a wide-spread abdominal manifestation as the cause of the suspected abdominal pathological process. (2) In diabetic coma vomiting usually precedes the pain, while in pre-coma cases with surgical complications the pain usually precedes the vomiting. (3) When appropriate therapy is applied, signs and symptoms due to acidosis clear promptly, while those of surgical conditions usually progress. The various possibilities as to the cause of the pain are discussed. Dilatation of the stomach is dismissed with the statement that it is common knowledge that gastric dilatation does not produce a true spasm of the abdominal muscle, and that while it does produce discomfort, rarely if ever does agonizing pain result. Hepatic engorgement was also suggested as an explanation, which scarcely seemed to be an adequate reason, since engorgement of the liver as seen clinically, rarely if ever produces a syndrome comparable to that under discussion. Dehydration fails to explain all the facts except that it is an early finding in many precoma cases, the majority of whom certainly present no similar abdominal signs or symptoms, and when dehydration is found in other clinical conditions such signs and symptoms are not observed. In the case reported it would scarcely seem that acidosis be the cause of the pain since acidosis persisted after the pain subsided. It is further suggested that the Insulin was scarcely the sole factor in controlling the symptoms, since a blood sugar of 380 was found after the symptoms had entirely disappeared.

The condition described by Edsall called heat cramp is discussed and attention invited to the fact that this condition is apparently in some way associated with chloride deficiency and that the administration of salt solution not only promptly controls the symptoms but will prevent them. The further emphasis on the possibility of the case reported having something to do with chloride deficiency is refernce to the condition known as "gastric tetany," which is associated with pyloric obstruction and characterized by vomiting and not only abdominal pain but also pain in any group of muscles that are vigorously exercised. As an explanation of abdominal pain in acidosis it is suggested that the chain of events producing the abdominal symptoms probably develops in the order of improper fat oxidation, acidosis development, nausea and vomiting, the depletion of body chloride because of loss of hydrochloric acid, the exercise of the abdominal muscles as the result of the vomiting, hence the pain and hence the relief offered by the administration of sodium chloride solution intravenously. It is admitted that these are merely postulates in this case because no blood chloride determinations were made, but it is suggested that such determinations might not have been a true index to the total body chloride, as plasma chloride may remain normal while the chloride content of the body as a whole may be markedly reduced.

Virgil E. Simpson, Louisville.

GAUSS, HARRY.

The Interrelationship of Gastro-intestinal and Renal Disease. Ann. Int. Med., IX, 1373, April, 1936.

Attention is invited to a relatively small group of cases in which a differentiation between diseases of the kidney and diseases of the gastro-intestinal tract are difficult. The anatomic, neurologic and metabolic relationships between these systems is offered as an explanation of reference of symptoms from one system to the other. The juxtaposition of the kidney to the liver, the duodenum, the hepatic flexure of the colon, the stomach, the spleen, the pancreas and descending colon are offered as reasons for the anatomical relationship.

The nerve supply of both these systems contains autonomic fibers of both vagal and sympathetic types and which have passed for the most part through the celiac plexus. The balance that is normally maintained as to the proportion of certain substances which are excreted in the stools or in the urine is offered as some explanation for the metabolic relationship. No adequate explanation is offered for the exact mechanism involved in these interrelationships that conceal the secret of functional disturbances set up in one system as a result of a diseased process located in the other. These reports are given to illustrate examples of renal disease that presented essentially gastrointestinal symptoms in the author's experience. The discussion closes with the following postulate. 1. The renal and gastro-intestinal systems are related anatomically through their juxtaposition and their ligamentous attachments and neurologically through their common innervation. 2. The following renal disorders have been reported as being common sources of gastro-intestinal symptoms: stricture of the ureter, hydronephrosis, movable kidney, pyelitis, stone. 3. In these conditions examination of the urine may reveal no definite abnormality and therefore be of no aid in diagnosis. 4. Physical examination may be helpful in eliciting characteristic pain or tenderness on palpation of the kidneys or ureters where they cross the pelvic brim, or at the lower ends within the broad ligaments. 5. A definite diagnosis can usually be established by means of ureteral catheterization and urograms.

Virgil E. Simpson, Louisville.

LEARY, TIMOTHY.

1. Atherosclerosis—Special Consideration of Aortic Lesions Archives of Pathology, 21:4, p. 459, April, 1936.

The author concludes from a carefully conducted study of human material obtained at autopsy that all the lesions of aortic atherosclerosis, save early mucoid changes in the intima, are due to the presence of cholesterol. The lesions are primarily intimal and depend for their nutrition upon imbibition through the endothelium. Variations in the structure and appearance of the lesions depend upon the age of the subject and of the lesions themselves. In youth atherosclerosis of the coronary arteries is marked by an increase of subendothelial connective tissue. It is loose textured, possesses no collagen, and is associated with small groups of lipoid cells (lipophages). In the fourth and fifth decades of life collagen formation takes place and results in the production of true scar tissue. In old age lipoid cells accumulate in masses with scant fibrous tissue, and because of failing nutrition necrosis takes place with the formation of atheromatous abscesses. Occlusion of the vessel lumen in youth is due to thrombosis following an acute fibrinous necrosis in the subendothelial layer which extends to the endothelium. In old age occlusion is due to the rupture of an atheromatous abscess into the lumen.

In youth the young fibroblasts metabolize the lipoid and, without an accompanying formation of collagen, minimal scarring takes place. As age advances, cholesterol metabolism within the lipoid cells is slowed, collagen is formed and heavier scar tissue is produced. With failing nutrition through the scar tissue the deeper layers necrose and secondary atheromatous abscesses are formed. In old age cholesterol metabolism ceases, lipoid cells accumulate in masses, nutrition to the area fails, and a primary atheromatous abscess results. The lesion in the ascending arch of the aorta does not follow this rule. Cholesterol metabolism continues unabated in this part of the vessel and the connective tissue formed remains as in youth, which results in minimal scar formation. Calcification arises in connection with necrobiasis or after necrosis has developed and marks the sites formerly occupied by living tissue. Factors, such as hypercholesteremia, thyroid secretion and iodine, age, stress, infection and injury, and toxic factors are discussed, but are held to be factors which influence only the deposit of cholesterol within the artery wall. The nutrition of the lesion within the wall the author believes to be wholly by imbibition from the blood stream through the endothelium. He denies to the vaso vasorum any influence in the process. The paper is profusely illustrated with beautifully prepared microphotographs.

In the second paper the author reviews the criticisms of experimental evidence pointing to cholesterol deposition as being the cause of atherosclerosis in man and reiterates the evidence of its being the only etiological agent at work. These arguments need not be summarized in this review. In the reviewer's opinion the whole question of the etiology of human atherosclerosis remains much as it was before. The cause or causes remain obscure and are probably varied in nature.

N. W. Jones, Portland, Oregon.

WATSON, W. L., AND BANCROFT, F. W.

Hypertrophic Cricopharyngeal Stenosis. S. G. O., Vol. 62, No. 3, pp. 621-624, March, 1936.

The authors report in considerable detail a case of a middle aged woman who presented a benign tumor of the cricopharyngeus muscle due to hypertrophy and degeneration of its fibers together with intracellular edema. The syndrome of which the patient complained caused the authors to diagnose upper esophageal obstruction due to a parathyroid tumor or an atypical thyroid tumor.

At operation the condition was thought to be an inoperable neoplasm. The tumor was sectioned longitudinally down to the mucosa, in much the same manner as was described by Rammstedt in relation to the hypertrophic pyloric sphincter, and a segment of tissue removed.

The post-operative course was stormy incidentally, but the patient recovered completely and is now well.

Eight figures accompany the article.

Nelson M. Percy, Chicago.

OCHSNER, A., GAGE, M., AND HOSOI, K.

Treatment of Peptic Ulcer Based on Physiological Principles. S. G. O., Vol. 62, No. 2-A, pp. 257-274, Feb. 15, 1936.

The authors point out a group of factors in proper sequence and combination as a possible cause of chronic peptic ulceration. They are divided into the uncontrollable group and the controllable group. The former group of factors which in reality are predisposing causes are: (1) tissue susceptibility and (2) constitution predisposition. They represent inherent qualities of the organism and are neither alterable or controllable. The latter group of factors, which may be called precipitating factors, are controllable and amenable to treatment. They are hypersecretion and hyperacidity, focal infection and gastric trauma.

From a series of shunting experiments the author concludes that hypersecretion and hyperacidity are the most important precipitating factors. Gastric trauma is probably the least important of them. Hypersecretion is best controlled by establishment of a normal pyloric function, the avoidance of certain activities which increase gastric acidity and secretion—smoking, especially of cigarettes, ingestion of alcohol and condiments. Neutralization of the gastric acidity is best accomplished by frequent small feedings. Calcium carbonate is the best alkalic for that purpose.

All foci of infection must be removed. Only a bland diet containing no roughage should be allowed.

The surgical treatment of peptic ulcer consists largely of the treatment of complications, such as mechanical obstruction, perforation, repeated hemorrhages, and danger of malignant change.

Gastro-enterostomy is the operation of choice in cases of pyloric obstruction with hypoacidity. It should not be done in cases with marked hyperacidity because of the increased susceptibility of the jejunal mucosa to the acid gastric chyme. In those cases gastro-duodenostomy is preferable. The chronic calloused ulcer in the stomach which does not readily respond to medical treatment should be operated upon and radical resection done.

Ten figures and a large bibliography accompany the article.

Nelson M. Percy, Chicago.

SHALLOW, T. A.

Combined One Stage Closed Method for the Treatment of Pharyngeal Diverticula. S. G. O., Vol. 62, No. 3, pp. 624-633, March, 1936.

As a matter of definition and for the sake of clarity and the advancement of our knowledge of pharyngeal diverticula, the author points out that there are no recorded cases of true pulsion diverticula of the esophagus. The reported cases of diverticula of the esophagus are traction diverticula; all reported pulsion diverticula have been pharyngeal in origin. In support of this view the work of Killian, Mognihan and Jamison is cited. The anatomical work of Killian and Jamison showed a small area of weakness in the pharyngeal wall. That area is a "slit between the pars fundi-formis of the cricopharyngeus muscle and the upper circular fibers of the esophagus. In this slit the recurrent nerve passes through to divide into the anterior and posterior branches." A branch of the inferior thyroid artery and vein and a bundle of lymphatic vessels passes through this biatus. The presence of the recurrent laryngeal nerve in this area explains the symptom of hoarseness which was present in nine of the authors cases. The presence of a larger resistant artery there may explain the occasional double diverticula seen. A diverticulum can arise from any portion of the pharynx which is perforated by a branch of the inferior thyroid artery. The most common areas are: Most fre-



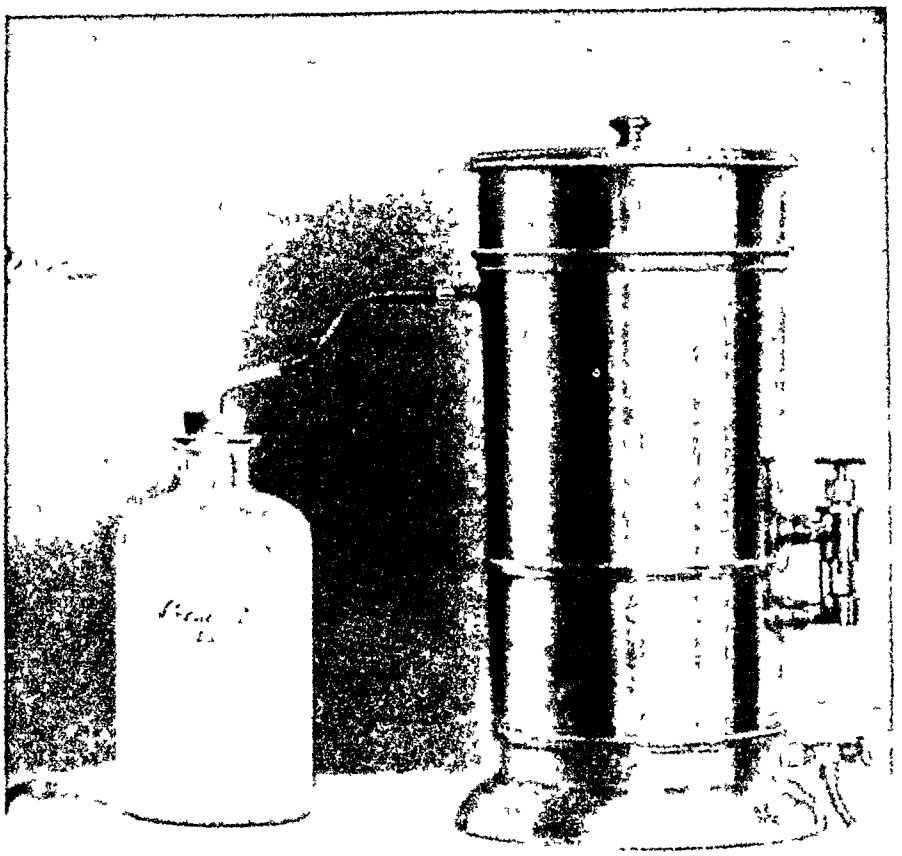
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The Creamalin Automatic Drip Control now makes a simple routine of the continuous drip treatment of peptic ulcer with colloidal cream of aluminum hydroxide (Creamalin). •• The continuous acid adsorption method apparently represented, on the basis of results reported, a superior therapy in peptic ulcer. Its application was limited, however, because of difficulties encountered in attempting to effectively administer the neutralizing agent as a continuous drip. The Creamalin Automatic Drip Control has entirely overcome these limiting factors and the gastroenterologists now have at their disposal an apparatus that permits a routine institution of this treatment. •• **THE CONTINUOUS DRIP METHOD** Winkelstein[1] first reported on the continuous neutralization method. Woldman and Rowland[2] later reported on a continuous neutralization method that utilized an adsorptive agent. Cream of colloidal aluminum hydroxide (Creamalin) is especially suitable as a neutralizing agent, as one volume will combine with 14 to 25 times its own volume of tenth normal hydrochloric acid by physical fixation without any dangers of alkalosis and without toxic effects of any kind. •• Woldman and Rowland, summarizing their experience, reported that by this method symptomatic relief is usually prompt, and x-ray evidence shows that an ulcer niche may completely disappear in seven days. A constant achlorhydria is produced as evidenced by frequent day and night sampling. The method is entirely compatible with any type of dietetic treatment. There is very little discomfort, and functional rest of both the secretory and motor function of the stomach may be allowed in larger measure during the period of healing. •• **DESCRIPTION OF THE CREAMALIN AUTOMATIC DRIP CONTROL.** This consists of a cylindrical metal container with three compartments, and a single glass bottle whose outlet is connected by a long rubber tube to an indwelling Levin tube. The rate of flow of the drops is controlled by a sight



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[1] Winkelstein, Asher: A New Therapy of Peptic Ulcer Am J. Med Sci 175 695, May, 1933

[2] Woldman, Edward E., M D and Rowland, Vernon C., M D: Continuous Acid Adsorption by Aluminum Hydroxide Drip in the Treatment of Peptic Ulcer The Review of Gastroenterology, Vol. 3 No. 1, p. 27-35 (March, 1936)

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quently from the commonly described area above the cricophahyngeus muscle; more often on the left side. The next place in the order of frequency in the authors series of cases was the Killian-Jamison area below the cricopharyngeus muscle. The location least frequently found to be the point of origin of these diverticula has been through the lower portion of the inferior constrictor muscle, a site for another branch of the inferior thyroid artery.

The symptoms of pharyngeal diverticulum are difficult and noisy deglutition, vomiting, hoarseness and occasionally a tumor palpable in the neck. The diagnosis is established by X-ray examination or by esophagoscopy.

The prognosis in this condition is much better than it was some years past. The condition is recognized earlier today.

The author is distinctly not in accord with those who advocate the two stage operation because of the probability of mediastinitis following a one stage operation. He is of the opinion that mediastinitis has been a rare complication in recent years. In his series of 76 cases there were 2 deaths, one from uraemia, the other from pneumonia. Pulmonary complications not infrequently follow the operation.

A detailed account of the authors technic is given.

Eight figures and a bibliography accompany the article.

Nelson M. Percy, Chicago.

ROSENBLATE, A. J., GOLDSMITH, A. A., AND STRAUSS, A. A.

A Summary of Regional Ileitis. J. A. M. A., Vol. 106, pp. 1779-1780, May 23, 1936.

For the past thirty years a number of granulomatous lesions of the intestine have been mistaken clinically for malignant or appendicial lesions. In 1932 they were described as a regional ileitis, and a year later as a cicatrizing enteritis.

The etiology of the condition is not known, but infection, especially anaerobic, is a possible cause. The pathologic lesion is a proliferation of the somatic cells of the intestinal wall and the hematopoietic cells. The coats of the intestine are edematous and thickened; the mesentery is thickened and the glands hyperplastic. The lumen gradually becomes narrowed because of fibrostenosis. Frequently there is perforation with localization of a mass in the right lower quadrant.

Microscopically, there is an acute, sub-acute or chronic inflammatory reaction with giant and epithelioid cells present.

Clinically, it is characterized by a low-grade fever having periods of normalcy, diarrhea containing mucus and occult blood, anorexia with loss of weight and secondary anemia, dull cramp-like pain in the right lower quadrant, moderate leukocytosis and rapid pulse. Stenosis occurs in the later stages.

X-ray after an opaque meal shows filling defects proximal to the cecum, abnormal contour of the terminal loop of the ileum, and dilatation of the ileac loops just proximal to the lesion.

The treatment is surgical removel of the diseased areas of the intestine with later anastomosis.

Francis D. Murphy, Milwaukee.

BARENBERG, LOUIS H., LEVY, WALTER, AND GRAND, MILTON J. H.

An Epidemic of Infectious Diarrhea in the New-Born. J. A. M. A., Vol. 106, pp. 1256-60, April 11, 1936.

Infectious diarrhea is a condition characterized by sudden onset, slight fever, dehydration, and complicated by upper respiratory and middle ear infections. No specific etiological agent has been isolated to account for this syndrome and there is no characteristic pathology in the gastro-intestinal tract.

Epidemics of this syndrome have in the past been reported on two occasions. Within the last year four such

epidemics have been reported in New York City institutions.

This is the report of an epidemic occurring in Morrisania Hospital in 1935. Of 43 infants in the nursery at the time of onset, 32 developed the disease. Fourteen of these babies died. The morbidity then was 74 per cent and the mortality, 43 per cent.

All the babies were normal, healthy infants previous to the onset. All patients showed a low grade fever never going higher than 103. Diarrhea was present almost from the onset in all cases. There were about six stools per day and all were markedly acid in reaction. Vomiting was present, but only in a few of the cases. The average weight loss in infants who recovered was about eight ounces, was gradual and occurred mainly in the heavier babies. In those who died the loss was about 23 ounces and was accompanied by severe dehydration.

The age of onset varied from two to twenty days. The fact that the onset was so soon after birth indicated a short incubation period.

All the babies affected were isolated, sterile, technique was instituted and all possible sources were cultured for etiologic agents, but none was found. They were treated so as to prevent dehydration and nutritional disturbances. Only in cases of severe vomiting was a period of starvation instituted and in only the most severe cases of vomiting was gastric lavage done. They were given 15 c.c. of protein milk with 3 per cent of carbohydrate alternating with one ounce of 1 per cent saline solution. In addition, 5 min. of epinephrine 1:1000 solution was administered hypodermically every three hours to prevent circulatory collapse.

Necropsy did not show a pathogenic picture in the gastro-intestinal tract to indicate a primary intestinal infection.

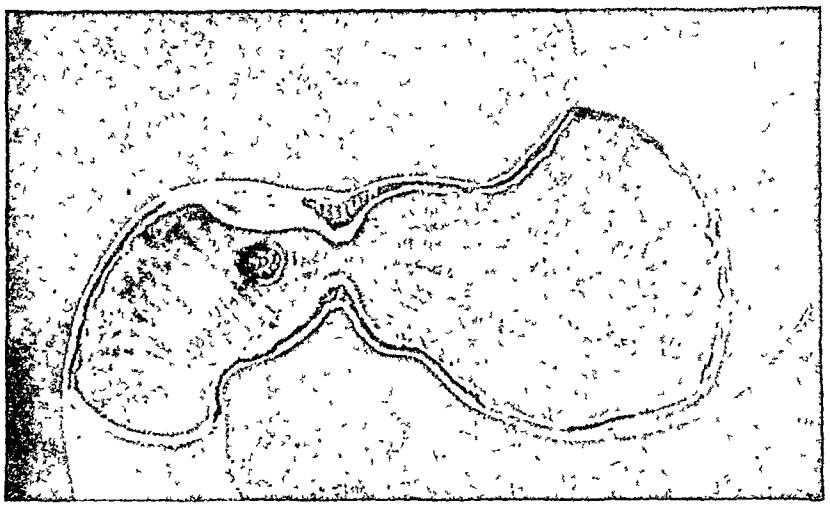
Francis D. Murphy, Milwaukee.

NUTRITION

GOLDZIEHER, MAX A.

Chronic Hypoglycemia. Endocrinology, Vol. 20, No. 1, 1936.

One of the most valuable features of this contribution is a classification of the different types of response obtained to the glucose tolerance test in a large group of chronic hypoglycemics. Goldzieher was able to distinguish 6 rather distinct types of response, as follows: (a) low fasting level, normal rise and return to the fasting level; (b) low fasting level, small rise and return to the fasting level; (c) normal fasting value, no rise and slow consistent below the fasting level (this type was twice as common as any of the other types); (d) low normal fasting value, small rise and substantial terminal drop; (e) low fasting level, sudden high rise, slow return and deep terminal drop (diabetic type); (f) very low fasting level, fairly good rise and early drop to a low point. All these types are found with equal frequency except (c). The actual causes of hypoglycemia are apparently many and of wide spread type, for only about 80% can be referred to hyperinsulinism, and the others are referred to liver damage and extra-pancreatic endocrine factors. Of the types said to be of pancreatic origin, roughly 28% were associated with diseases of the pancreas and the balance regarded as functional hyperinsulinism. The surgical removal of normal pancreatic tissue in patients for the relief of hypoglycemic symptoms proved to be a great clinical disappointment. The reviewer remembers that Banting showed several years ago that a dog could not be rendered diabetic even by the massive injection of glucose so long as even a very small portion of the pancreas remained. It is now practically certain that many hypoglycemics with symptoms of a disagreeable nature owe their trouble to endocrine disturbances other than pancreatic overfunction, just as we believe that many persons with chronically low



DIET-ALKALI *versus* LAROSTIDIN

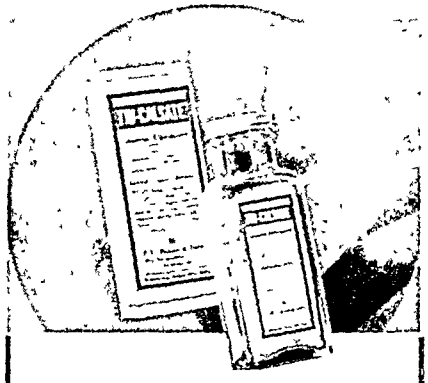
The Sippy treatment, in its various modifications, is so restrictive as to be irksome to many ulcer patients. They find life a sorry burden.

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It has been demonstrated*, moreover, that 70% of the diet-alkali failures make a favorable response to Larostidin. It would seem advisable to start ulcer patients on Larostidin right away

**Journal A.M.A.*, April 25, 1936, page 1457

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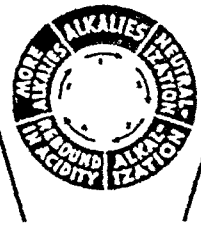
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basal metabolic rates owe their biochemical pattern to disturbances other than hypothyroidism. In the true organic hyperinsulinism due to fibroid and adenoma and cancer of the pancreas, relief may be expected from surgical intervention to the same degree as in toxic lesions of the thyroid. The other cases disassociated from organic or 'functional" pancreatic disorder form at present an attractive field of romance. The most common clinical manifestations of hypoglycemia were found to be: abdominal pain, excessive hunger or craving for carbohydrates with coresponding obesity, mild or severe fainting spells and tachycardia. Epileptiform seizures, speech defects and dysmenorrhea were also observed. Probably insufficiency of the pituitary and thyroid may eventually be found to be factors in many of the obscure cases. Lee Martin's paper given at the 1936 meeting of the American Gastro-enterological Association indicated that hypoglycemia is a bewilderingly broad subject in which known factors are yet in the minority.

Beaumont S. Cornell, Fort Wayne.

THERAPEUTICS

WOSIKA, P. H., AND EMERY, E. S.

The Effectiveness of the Sippy Regimen in Neutralizing the Gastric Juice Patients if the Amount of Alkali is Not Varied. Ann. Int. Med., Vol. 9, No. 8, pp. 1070-1077, Feb., 1936, and The Value of a Mixture of Powdered Milk and Alkali for Neutralizing the Gastric Acidity of Patients with Peptic Ulcer, ditto, pp. 1078-1090.

In 46 patients with duodenal ulcer receiving the routine Sippy treatment 30 minute day-long tests of gastric juice samples were made under strict Sippy rules, varying from milk and cream only to "first day," "seventh day" and "fourth week" procedures. The free acidity was adequately controlled in more than one-half the patients and symptoms were entirely abolished in all cases. The data indicate that if the free acidity does not rise above 20 after an alcohol test meal, the patient will obtain adequate control by this method. There seems to be no criteria to determine which patients will be controlled in the large group whose free acidity does go higher than 20 following an alcohol test meal. Calculations suggest that 25 to 50 times more alkali was given than should be necessary theoretically. If a routine treatment is used, one can be assured of complete neutralization only if frequent aspirations are performed.

It was found that 12.5 gm. of a preparation of powdered milk mixed with the usual Sippy powder containing 0.6 gm. of calcium carbonate and 2.0 grams of sodium bicarbonate, and given at intervals of one hour are somewhat more effective in neutralizing the gastric acidity than 90 c.c. of milk and cream and the same powder given in the usual way advised by Sippy.

Beaumont S. Cornell, Fort Wayne.

KLUMPP, THEODORE G.

The Treatment of Pernicious Anemia with Autolyzed Liver Concentrate. J. A. M. A., p. 1245, April 1, 1936.

Reimann in 1931 noticed that the antianemic potency of fresh liver was increased by digestion in normal human gastric juice. Similar results have been reported by various investigators. Herron and McEllroy suggested that a similar enhancement of potency could be obtained by autolysis. This was further influenced by Wills, who found that ordinary yeast was inert, while autlyzed yeast was effective in the treatment of tropical macrocytic anemia.

The authors tried the therapeutic potency of autolyzed liver concentrate—Squibb (N.N.R.) for a period of two years, at the New Haven Hospital. They came to the conclusions that autolyzed liver concentrate is effective in the initial and maintenance treatment of pernicious anemia, that it is more potent than liver extract—Lilly, from the same amounts of liver, that the initial dose to produce maximal effects is that obtained from autolyzed liver concentrate derived from between 150 and 200 of liver, and that the maintenance dose was between one and eight teaspoonsful daily and averaged three teaspoonsful.

Francis D. Murphy, Milwaukee.

VINSON, P. P.

The Treatment of Carcinoma of the Esophagus. S. G. O., Vol. 62, No. 5, pp. 840-842, May, 1936.

The surgical treatment of carcinoma of the esophagus has been disappointing because of the formidable nature of the operation and the highly malignant nature of these tumors. Roentgen Rays and Radium have proved to be of little or no benefit because of the added discomfort they cause the already distressed patient. Electrocoagulation of the mass through the esophagoscope gives promise of being a useful procedure. Intubation of the growth may be accomplished by passing a suitable tube over a previously swallowed silk thread.

Palliative gastrostomy and mechanical dilatation of the stricture are the most widely practiced palliative procedures. If the condition of the patient will not permit gastrostomy, dilatation of the stricture may afford relief for a period of from six to eight weeks. Further dilatations will continue this benefit for an indefinite period.

In the rare cases of esophago-bronchial or esophagotracheal fistula dilata-

tion should not be attempted but recent haemorrhage the author considers, is not a contraindication to dilatation.

Five figures accompany the article.

Nelson M. Percy, Chicago.

ABDOMINAL SURGERY

WOLFSON, W. L., AND ROTHENBERG, R. E.

Acute Noncalculous Cholecystitis. J. A. M. A., Vol. 106, pp. 1978-1980, June 6, 1936.

During the past ten years Wolfson and Rothenberg have operated on 379 cases of acute cholecystitis. Of these, 31 were diagnosed as non-calculous cholecystitis, which diagnosis was confirmed at operation.

In going over these cases it was found that the incidence of acute non-calculous cholecystitis in this series was 8.2 per cent; 58 per cent of the cases occurred in men.

The usual symptoms of gaseous eructations, aversion for fatty foods, and a history of previous attacks is not characteristic of these cases. The disease, however, is characterized by a higher temperature range, greater incidence of chills, greater morbidity and a greater incidence of perforation than other forms of acute cholecystitis. The etiology of the condition is believed to be a hematogenous infection rather than an obstruction in the cystic duct.

Francis D. Murphy, Milwaukee.

KNIGHT, J. C., AND SLOME, DAVID

"Intestinal Strangulation." Brit. Jour. Surg., 23:820-854, April, 1936.

This report deals with the results of a comprehensive experimental study and careful review of the literature. In considering statistical tables, all showing a high mortality in large series of cases of acute intestinal obstruction, the great lesson learned is the extreme urgency of the earliest possible diagnosis and treatment in reducing that mortality. The particular interest in this study was the segregation of those cases of intestinal obstruction without circulatory involvement (due to neoplasms, gall stones, foreign bodies, band compression, etc.) from those of acute intestinal strangulation (due to volvulus intussusception, hernia, etc.) where the essential pathological feature is venous strangulation of the intestine.

Most previous experiments to find the cause of the toxemia developing in both types of cases have been done with occluded but not strangulated loops of intestines. Various factors found to play a part were nervous reflex action, bacterial invasion, distention, dehydration, hypochloremia, and toxic substances developed within the bowel wall or bowel lumen. The striking rapidity of the appearance of collapse in cases of intestinal strangulation would eliminate many of the factors which could well explain the slowly developing symptoms in non-strangulating obstruction—for instance, in strangulation death may take place before there is any appreciable drop in blood chlorides. It is the opinion of the authors that there is produced in the gut wall in severe strangulation a depressor substance. This substance can be demonstrated in the wall and in the peritoneal fluid within an hour and even within the thoracic duct in forty to seventy minutes. It is this substance which accounts for the great fall in blood pressure. Less definite evidence is offered in reproducing the symptoms by injection of this substance in normal animals. Accessory contributory factors that may play a part are the rhythmic alteration in distention and the length of the involved segment of bowel. Due to the fact that release of the strangulated bowel may pour into the circula-

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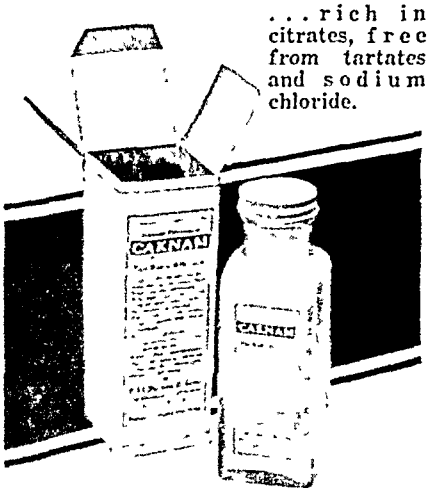
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tion large quantities of dammed up depressor substance, the question is raised as to whether resection rather than release of strangulated bowel may not prove to be the safest procedure. Whichever plan of treatment one follows, he will be impressed by reading this article *of the importance of earlier diagnosis* and treatment.

J. Duffy Hancock, Louisville.

FRANSEEN, CLIFFORD C.

Les Fistules Cholecysto-coliques Consecutives a la Lithiase. (Douriez-Bataille, Lille, France, 1936).

A 64 page monograph on the subject of cholecystocolic fistula gives a good review of the subject and presents in detail a new case of the author. . He shows that such fistula is practically always the result of gall stones, plus the factor of infection and the commonest mechanism is compressive ulceration by a large calculus. The production of the fistula may be accompanied by a most painful clinical episode or be absolutely unnoticed by the patient. After the formation of the fistula a period of symptom amelioration usually occurs only to be followed by symptoms due to the infection of the bile passages. While a diagnosis might be tentatively made from history and physical examination, reliance must be placed upon the use of an opaque enema to fill the gall bladder. The prognosis is always serious and surgery imperative. Cholecytectomy with suture of the colon gives 75% of cures. The case described by Vorhaus and Rogers in this Journal in April, 1934, is referred to.

Beaumont S. Cornell, Fort Wayne.

FLETCHER, H. N., AND CASTLEDEN, L. S. M.

"Three Cases of Duodenal Diverticulum Removed by Operation." Brit. Jour. Surg., 23:776-786, April, 1936.

Duodenal diverticula are either primary or secondary. The secondary are due to traction of some adjacent inflammatory process and invariably occur in the first part of the duodenum. The primary are more common, and occur generally at the concave inner aspect of the descending limb, only occasionally from the third and fourth portion and never from the first portion of the duodenum. They are thin walled hernia of the duodenal wall, consist of mucosa, submucosa, and possibly a few muscle fibers, are more frequent as age advances, and while usually solitary may be multiple. Perforation and even inflammation of the sac are very rare.

Cases are rather difficult to diagnose symptomatically. The pain is of the deep gnawing type or characterized by heavy discomfort in the epigastrium. The relation of the pain to the intake of food is indefinite. While there are periods of especial distress there is seldom complete disgestive comfort between attacks. The history is often a long one. Gastric flatulence and belching with only incomplete relief is suggestive. Vomiting, if present, may also be ineffectual in giving relief. Some tenderness in the region of the diverticulum was found in all three cases reported. Diagnosis will be established by the X-ray. The treatment in view of the rarity of inflammation and perforation should be non-surgical at first. If the digestive symptoms persist, stasis can be demonstrated in the diverticulum, and other possible causes can be excluded excision should be done. This was not difficult in the three cases under consideration and the results obtained were most satisfactory, absolute relief in the two uncomplicated cases and great improvement in the third where the diverticulum was accompanied by a pyloric adhesion.

J. Duffy Hancock, Louisville.

FRANSEEN, CLIFFORD C.

Gastrostomy Feeding. J. A. M. A., Vol. 106, pp. 1373-1376, April 18, 1936.

The gastrostomy diets used in most hospitals, both large and small, are usually very deficient in the caloric requirement of the patient. They usually consist of milk, eggnogs, malted milk, broth, cream and lactose.

Clinically it has been observed that lactose will cause diarrhea and flatulence, while experimentally it has been observed that from 40 to 50 per cent was lost so far as weight or energy relationship were concerned in the rat.

The diet recommended here consists of seven-and-one-half cups of oatmeal gruel to which corn syrup, melted butter, baby vegetable puree, brewer's yeast powder and table salt have been added, in addition to five poached eggs pushed through a fine strainer.

A special feeding consisting of strained orange, tomato or grapefruit juice, beef scrapings, iron and halibut liver oil is also given.

The feeding schedule is as follows:

1. One-and-one-fourth cupsful of feeding mixture at eight, twelve, two, four, six and eight o'clock.

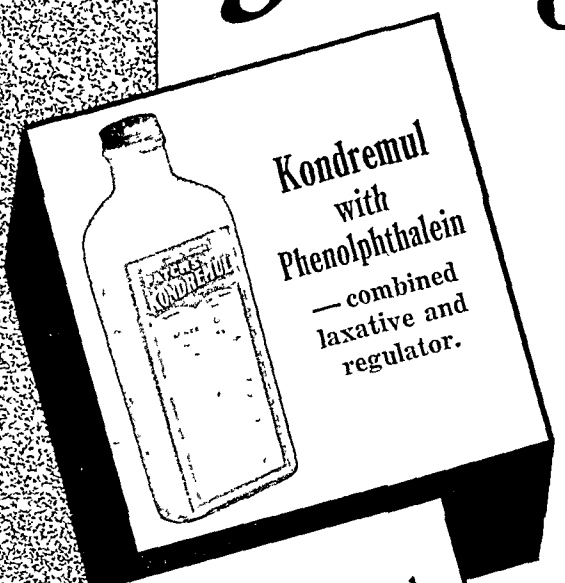
2. Special feeding at 10:00 A. M.

The first twenty-four hours after operation nothing is given by tube so that the sinus tract will become walled off. Supplementary fluids of 10 per cent glucose or saline are usually given the first three days.

Cereal and vegetables are not given until the full diet is adopted. The quantity of the feedings is gradually increased, until by the eighth day the full diet mixture can be given.

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"... we know that in the infant and growing child alkali in excess of acid must be stored."

Growth and Development of the Child, Part III, White House Conference on Child Health and Protection, New York, 1932, p. 213.

BUT— many diets are acid-forming

AS pointed out in the Journal of the American Medical Association (Queries and Minor Notes, 103:701, 1934), "... most high carbohydrate foods of the artificial and refined types are lacking in the basic elements. These basic ions, such as sodium, potassium, and calcium, are necessary for the neutralization and excretion of the various acid waste products of the body. Hence carbohydrates may be implicated in the occurrence of such an acid state by displacing other necessary food products from the dietary."

Ordinary cereals and cereal products, meat, and eggs—all produce an acid ash when burned in the body, yet they form the mainstay of the average diet. Although this preponderance of acid-forming foods is not definitely known to have great significance for the health of normal adults, a number of authorities advocate a basic or alkali-forming diet for children and pregnant women.

INFANCY AND CHILDHOOD. "Alkaline diets are essential for infancy where growth is rapid," declares Shohl. He calculates the need as 10 cc. excess of 0.1 normal base per kilo per day.[1] Babies fed on breast milk stored an excess of base over acid, the range being from 31 to 56 cc. 0.1 N base per day, is the finding of the Committee on Growth and Development of the White House Conference on Child Health.[2] Lippard and Marples observed greater increases in weight of infants receiving basic diets as compared with controls on acid-forming feedings.[3]

PREGNANCY AND LACTATION. Shohl states, "Pregnancy and lactation require additional alkali—a minimum of 150 cc. 0.1 N base per day."[1] Coons and associates, from acid-base balances taken upon normal pregnant women receiving basic diets, determined that the storage of basic substances was even greater than estimated by Shohl. "This may be some indication," they say, "of the magnitude of the maternal needs exclusive of fetus."[4]

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[1-4] *Bibliography on request.* *Mead's Cereal (Pablum in uncooked form) is also base-forming.

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Cornmeal		5.3
Barley		10.1
Rice		8.1

Figures given in the above table are based on 100 grams of food and represent cubic centimeters of normal acid or base.

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SECTION I—*Clinical Medicine: Diseases of Digestion*

A Classification of Gastro-Duodenal Ulcers on the Basis of Their Etiology*

By

SAMUEL C. ROBINSON, M.D.
CHICAGO, ILLINOIS

THE progress of science in the past has, in a great measure, been aided by classification. This has involved the gathering together of a large mass of data followed by the orderly grouping of kindred facts into separate divisions. It was natural that the early groupings in any single branch of science were large and inclusive in their content. But knowledge is not a static thing nor should the earlier made classifications, based on incomplete knowledge, remain static. In the light of further development and discovery, it is often necessary to break down the material into smaller sub-divisions and to shift some data from one group to another where they are later seen more logically to belong. This process of regrouping and reclassifying, of adding and subtracting until the kinship of each division becomes more definite and clear, contributes greatly to the general understanding of the subject. In all fields this process continues if we are willing to view each new development with objectivity and decline to cling to older classifications simply because they were the original ones or through our misguided attempts to do honor to their worthy protagonists.

Even in the face of newer knowledge and continuous changes in our classifications and theories, it is surprising how many of the outworn interpretations cling to the literature. It is difficult to dislodge them because repeated acceptance by great, though now deceased, authorities in their respective fields lends such prestige to these interpretations that the newer man with less weight of authority to his writing scarcely dares even to challenge them. The fact that in the earlier hypotheses there is often a kernel of truth, though this be encrusted with many irrelevant facts, makes it more difficult to get the whole subject reopened for critical consideration. This situation is most true in the field of medicine which is as yet the least exact of all the biological sciences; the field of gastro-enterology is no exception (1).

Let us consider the mere matter of nomenclature in gastro-duodenal disease.

The very term "peptic" is in itself a misnomer. The term arose years ago when it was thought that all ulcers were located in the stomach. It was therefore natural that the term "peptic" should be used to designate those ulcers. It was short and referred to those erosions originating in the areas of peptic cells. The term had an added connotation of a digestive process and gave implications of etiological significance. A "peptic" ulcer was one that occurred in the mucosa of the stomach lined by pepsin-secreting cells and was supposed to be the result of a process of self-digestion of an enzymic nature. Soon after the discovery of the Roentgen ray it was revealed that most of the ulcers that were supposed to be in the stomach were in reality located in the duodenum. The clinical picture of the two ulcers was the same and it is easy to understand why they were grouped together. Even now with a clearer understanding of these disease entities, differentiation is difficult. The term "gastric" is used interchangeably with "duodenal" and only the keen clinician possessing a well grounded understanding of the history and physical findings and a familiarity with the anthropometric differences of the two types is able to make the differential diagnosis successfully (2). So it is easy to see how these two differently situated ulcers were considered as one, and gastric in location.

Fifty to one hundred years ago the autopsy was the main source of histopathology and its relationship to clinical findings. And it is a well known fact, substantiated by pathologists generally today as well as in Virchow's time, that the incidence of gastric ulcers in autopsy material is greatest, whereas clinically the duodenal type of ulcer outnumbers the gastric about ten to one (3, 4). The X-ray gave this subject a tremendous impetus and revealed to the amazement of the older clinician that what was formerly considered a peptic or gastric lesion was in reality a Brunner's or duodenal lesion in the great majority of cases. But the name stuck to this very day to confuse us and give false implications of its site and etiology, for most ulcers are not peptic in their location nor are they caused by self-digestive enzymic action. "Brunner's ulcers" would be more appropriate but the same objection holds here, namely attention is focussed on the nature of the cell, in which the ulcer develops, which in itself has no relationship to the etiology of the disease, and further many ulcers are gastric in location.

However the duodenal and gastric ulcers do have these two important facts in common: First, embryologically the duodenum and stomach arose from the same *anlage* in the gastro-intestinal tube (the duodenum is in reality more a part of the stomach than it

*From the Department of Medicine, Woodlawn Hospital, Chicago, Illinois.
Submitted March 23, 1936.

is of the intestine), (5) and second, that portion of the gastro-intestinal tract where most ulcers develop, namely, the lesser curvature and the duodenum, receives the bulk of the nerve supply.

From the foregoing it would seem wise to drop from usage the term "peptic" in connection with gastro-intestinal ulceration.

ETIOLOGICAL BASIS OF CLASSIFICATION

Clinical versus Pathological. The classification, presented in this paper is made chiefly on a clinical and etiological basis rather than on a pathological one. Ulcers produced by the identical cause may show a great variety of pathological changes and infinite gradations of them, depending upon their age, chronicity, complications, etc. Ulcers of different groups may present about the same histopathology but as clinicians we are more interested in their classification *on an etiological and physiological basis than in the* end microscopic slide which often ignores these factors. Always in the past we have allowed the pathologist to dominate our thinking in the elucidation of disease. We had to square with his interpretation of dead tissue before we could proceed. This has applied to brain, heart, kidney, endocrine system, especially the thyroid, pancreas, to the gastro-intestinal system, and other viscera.

Internists especially interested in unfolding the emotional factors behind many organic diseases in these systems resent this restricting influence of the pathologist. His inability to show histopathological change in organs that we have seen to have positive clinical evidence of altered function and structural change merely speaks for the limitations in his field. We might quote a pertinent paragraph from Bentley and Cowdry's book "The Problems of Mental Disorder" (6). "Suppose that some physicist tomorrow invents a microscope with much greater useful magnification. At once abnormality may be seen where none was previously visible. But why confine ourselves to the microscope? Certainly there are other ways of recording abnormality of the human organism besides visual observation of fixed and sectioned tissue. For example, the spectroscope may show that a certain type of sugar is found in the urine of an athlete before a contest. This is an observation which may be recorded photographically; it is a phenomenon which can be shown to occur regularly; by chemical methods the sugar may be estimated quantitatively. The average histopathologist, nevertheless, will strenously maintain that there is no organic pathology in this anxious athlete and that the disease is 'merely functional.' What the histopathologist really means is that after an autopsy in this athlete no lesion would be visible in stained section of tissue, with a microscope of the type used in 1931." As physicians we must accumulate the clinical evidence that proves the relationship of psychic trauma to somatic disease. We may then hope that the physiologist and pathologist may set to work and reveal the *modus operandi* of the mechanism involved. In doing so the physiologist will have to abandon his laboratory animal. It would be well that some physiologists be made part of the "Department of Medicine" to catch up with what seems to be already proved by the internist. We must not subscribe to the statement that "In the history of medical research one finds over and over again that progress in the knowledge of the pathogenesis of a disease is made only after the disease can be reproduced in laboratory animals" (20). In the writer's opinion this can not be demonstrated for the following diseases: chronic gastro-duodenal ulcer, irritable colon, ulcerative colitis, thyrotoxicosis, neuro-circulatory asthenia, many degenerative diseases, etc. We must rely increasingly upon *human physiology* as Sir Thomas Lewis has urged so eloquently in the last few years. In the future we shall advance our knowledge of visceral function and pathological physiology chiefly through clinical observation.

Many clinicians today stand ready to give up the relationship of the pancreas to diabetes because the pathologist cannot find sufficient destructive evidence in the islands of Langerhans. This is gross submission to an illogical approach and shows the crushing *hold the cellular theory of disease has on us clinicians.* Can the pathologist tell us from a cross section of the nerve the number of impulses that are relayed to the cells in those islands? Can the pathologist tell us from the microscopic picture which cell in the island secreted one unit of insulin or portion thereof and which ten times that amount? Can he tell us much about the interplay of hormones? Can the pathologist tell us from the examination of ten specimens of human stomachs which one secreted 10%—20%—40% —or 80% of free hydrochloric acid? Which secreted a minimum, moderate and maximum amount of pepsin? Which were rich or poor in the intrinsic factor of pernicious anemia? Which of the stomachs, samples of which he holds in his hand and enjoys the privilege of seeing, feeling, dissecting, staining and subjecting to any chemical test, I repeat, which of these stomachs were hypertonic in life, hypermotile, which only moderately so and which exhibited atonia or excessive reverse peristalsis? Which showed, clinically, hypersensitiveness to emotional disturbances and which were calloused to them? Which of the stomachs were subject to altered autonomic control to produce vascular spasm, thrombosis and ulceration? When the pathologists can answer these questions they may be able to nullify clinical observations, but not until then.

These altered physiological manifestations of the gastro-intestinal tract constitute the earliest signs and symptoms of the sickness and distress for which seventy-five per cent of our patients see us. But the pathologist can as yet throw little or no light on the subject. The future may have a different story to tell, but until then we must, as clinicians, record our observations meticulously, make our deductions and advance our hypotheses for the etiology of disease and its rational therapy even in the face of the pathologist's ridicule (6). At a recent meeting one pathologist commenting on a paper dealing with the relationship of emotions to hypertension, said to the great amusement of the audience, "as pathologists we have as yet not found the seat of emotions."* Shall we shut our eyes to the obvious nervous instability in so many patients which causes pathological physiology and structural change manifested in nearly every

*In the opinion of many physiologists the seat of emotions has been found. The Diencephalon (hypothalamus)—"is the visceral component of emotional reaction and the sympathetic nervous system is under its control." (42)

organ merely because the pathologist has not as yet been able to locate its source? This is indeed worship of a false idol! We should like to stress the point that no attempt is being made to minimize the tremendous importance of pathology in the field of clinical medicine. Attention is being drawn to its limitations today especially in the field of emotions and bodily changes. We are glad to note that some pathologists subscribe to this viewpoint and that their number is increasing.

Inasmuch as our ultimate goal as physicians is the treatment of disease and this cannot well be attempted without an adequate knowledge of its cause, it seems desirable to formulate disease classifications from the etiological standpoint. The following classification of gastro-duodenal ulceration is made on this basis. It is not presented with any idea of finality, for we have seen before the need for constantly re-evaluating in the light of scientific advance, any classifications made. It is, however, presented as the most logical approach in the light of our present frontier of knowledge. Future explorations in the field may modify the classification here presented.

CLASSIFICATION OF GASTRO-DUODENAL ULCERATION

I. DIRECT
- a. Traumatic
  - 1. Internal
  - 2. External
- b. Chemical
- c. Malignant
- d. Infections
  - 1. Tuberculosis
  - 2. Syphilis

II. INDIRECT
- a. Psychogenic (common chronic ulcer; "Peptic" ulcer)
- b. Hemorrhagic erosions—caused by:
  - 1. Nephritis, with or without arteriosclerosis
  - 2. Acute and chronic infectious diseases
  - 3. Debilitating and degenerative diseases, arteriosclerosis, atherosclerosis, amyloidosis, etc.
  - 4. Post-mortem changes
  - 5. Vascular erosions due to cirrhosis of the liver, or any obstruction to gastric vessels—such as gall bladder disease, carcinoma, etc.
- c. Burns
- d. Brain Trauma—Especially to regions about the hypothalamus—tumors, inflammation, surgery
- e. Follicular ulcer
- f. Melena neonatorum

DIRECT ULCERS

The two major divisions of gastro-duodenal ulcers into Direct and Indirect makes clear the general lines of etiology. The Direct group of ulcers includes those that have their origin in the wall of the stomach and duodenum. No systemic factor is responsible for the lesions. Their etiology is to be found in the malignant, traumatic and chemical destruction of the wall itself where the process is initiated. This entire group constitutes but a small portion of all gastro-duodenal ulcers and emphasizes again that the greatest cause of these lesions comes from outside these structures just as we have learned that emesis and stomach disorders are in a great percentage of cases extragastric in origin.

a. Traumatic ulcers. The ulcers that follow internal and external trauma constitute a very small percentage of the Direct Ulcers. They are very acute and short lived and have no resemblance or relationship to the chronic ulcer.

Traumatic ulcers caused by the intake of sharp particles are very rare. Coarse food may cause a temporary break in the mucosa of the stomach but these heal very rapidly. Pins, tacks, glass or other sharp edged objects cause larger and deeper breaks but these, too, heal rapidly, the most classic example being the tack swallower in a side show of a circus. X-ray showed twenty-eight tacks throughout the gastro-intestinal tract with some in the stomach but no ulcers.

We have learned that if large portions of the mucous membrane and considerable submucosal structure of the stomach of animals are removed, chronic ulcer does not form. It does not matter how much acidity is present or even if acidity is added. The course is the same, namely, the ulcer heals rapidly, new mucous membrane bridging the defect.

The same is true in man. "Wounds of the human stomach made by surgeons heal rapidly" (7). Bullet wounds of the stomach, as the army physicians have learned so well during the World War, heal without producing a chronic ulcer (8). All of this evidence would tend to prove the reparative powers of the stomach, its ability to heal small and large abrasions and the fact that hydrochloric acid and pepsin act in no wise as deterrents to the healing process (9).

The injury to the stomach lining or submucosal structures from an external blow does not differ materially from a surgical injury or a bullet wound. There is very little in the line of destruction that a physical blow would accomplish that could not be duplicated by a bullet. There might be some undermining of layers such as the muscularis or mucosa, but it is difficult to see why this particular damage would be more conducive to the production of a chronic ulcer than any anatomical damage produced by a bullet. It might delay healing and cause some hypertonicity and hypersecretion but seldom if ever a chronic ulcer. Nearly all parenchymatous tissue manifests the same ability quickly to arrest any inflammatory or destructive process and even to lay down its particular new cells. This of course takes place in the special medium of the damaged tissue whether it be an acid, alkali, bile or enzymic solution (9). This is part of a simple law of evolution, namely, that highly specialized cells adapt themselves to their particular media. Surgical removal of pieces of liver, uterus, kidney, pancreas, and bowel is followed by quick healing usually by first intention unless complicated by infection. Off hand one would think that hydrochloric acid, pepsin, bile, enzymic solution from the pancreas, putrefactive material from the bowel and rectum would not be ideal solutions in which to bathe healing wounds with their delicate fibroblasts and mitotic cells. But wounds heal in all these media and often very rapidly.

Crohn (10) cites several patients who developed chronic ulcers following external traumata. The list

is small and only after a thorough search of the domestic and foreign literature is even this small number obtained. This alone speaks for the rarity of the condition which would strike one as unusual considering how common the chronic ulcer syndrome is in the general population namely, about 5% to 10%. As stated above, most ulcers caused by external trauma heal rapidly. If we do find in the very rare instance, that a gastro-duodenal lesion following external trauma persists and becomes a chronic ulcer in spite of the natural reparative tendencies of the organ, we must infer that there is some individual diathesis to the disease. External trauma to about 5% to 10% of the population who have a latent constitutional defect of their lesser curvature and duodenum might well produce a lesion here, not because of the trauma alone but rather due to the shock, the spasm and thrombosis that follow in susceptible individuals. It is interesting to note that nearly all of the cases cited in Crohn's paper are *along the lesser curvature* and duodenum where over 95% of the chronic ulcers *naturally* occur. The literature holds far *more* records of the sudden onset of chronic ulcer in patients who were in accidents *without* any trauma occurring to the stomach. Accidents, not entailing any bodily injury whatsoever, may precipitate a chronic ulcer. The shock alone in these latter cases is sufficient to initiate an emotional upset leading to the spasm of the vessels and ultimately to ulceration. One cannot overlook the factor of shock and the resulting disturbance of the emotional equilibrium in any violent blow to the abdomen. The best of us would have some emotional reaction and to those more sensitive, the accident might serve as a "trigger-release" setting loose an outflow of stimuli that could not be controlled before actual ulceration would be produced. To ascribe the formation of a chronic ulcer to trauma alone is to ignore the vast accumulated evidence of constitutional and personality uniqueness of the ulcer-type of patient which a blow cannot produce (2, 11). If we could find even a small series of cases in which a blow to the abdomen produced an ulcer along the *posterior* aspect of the stomach, where the psychogenic ulcer seldom if ever occurs, and in a short and stocky negress which type and race are practically free from the disease, we would say that the experimental evidence looked strong.

The absence of any gastro-intestinal disturbance prior to trauma does not exclude, entirely, the existence of ulcer. In some instances ulcers and scars in the gastro-duodenum are found in the operating room and at autopsy without any former history of dyspepsia. Nor does the absence of a dyspeptic history exclude the ulcer type of individual who as yet has escaped gastro-intestinal manifestations of his disease but is waiting for some "oppositional environment" to come along and permit dyspeptic response. This is our interpretation of most of the chronic ulcers following external trauma. In other words, trauma *per se* cannot produce a chronic ulcer.

Diaphragmatic hernia has been shown to produce gastric ulcer (36). This would seem to be due to external trauma and is therefore placed under this heading.

b. Chemical Ulcers. Strong alkalies or acids may produce ulceration but more often extensive scarring. The diet of some Ethiopian tribesmen, consisting of capsicum and peppers, produces ulceration of the stomach. Alcohol has been shown to produce lesions of the stomach. These ulcers are all very acute and subside when the offending irritant is removed.

c. Malignant Ulcers. The malignant ulcer is classified as belonging to the Direct Group rather than as being secondary to any chronic ulcer. It is presumed that there has been an hereditary transmission of a nest of cells in the stomach wall. At some predetermined time they abandon their dormant hybernating state and break out as a malignant growth. This is an independent process and has no relationship to any other diseased states of the stomach. The proof that malignancy takes place in any benign ulcer has not been established (12). The evidence is mostly against any such conclusion. Most ulcers occur in the duodenum, most malignancies in the stomach seldom in the duodenum. The site of most malignancies is along the posterior aspect of the stomach and the immediate prepyloric region (13), few chronic benign ulcers occur in these locations; they occur mostly along the lesser curvature. Malignancy is associated with low acidity or its entire absence; ulcer with its increase. The build of the ulcer patient is long and thin, that of the malignant patient may be of any type. There is also a difference in the age groupings at the time of onset in the two diseases. Carcinoma cuts across the lines of race, sex, age groups, build and personality types (48). Those who claim the relationship are on the defensive and must produce the proof. It is significant that those who argue for the malignant transformation of chronic ulcer have already reduced their recent estimates from 12% to 3%.*

d. Infections. Ulcers of the gastro-duodenum caused by bacteria are due in most instances to tuberculosis or syphilis. The clinical course of the ulcer itself may parallel the systemic disease. There may be some argument in favor of classifying these ulcers under the *Indirect* group inasmuch as the portal of entry of the organism probably is elsewhere than in the mucous membrane of the duodenum or stomach. The production of the ulcer, however, is due entirely to the intramural growth of the bacteria and the subsequent destruction of tissue to produce the erosion. While the bacteria may be secondary to some original focus the erosion is primary and independent of any systemic factor.

II. INDIRECT ULCERS

Most ulcers of the gastro-duodenum come under this classification. Causes from outside these structures, such as psychic, toxic, bacterial and so forth act to effect changes in the different layers of the stomach and duodenum. Systemic diseases of diverse kinds may, as an associated disturbance, leave their imprint on the vulnerable gastro-intestinal tract. The ulcers in this group are secondary to some other diseased process. They may be the major manifestation of a systemic condition as the chronic ulcer is, or most *incidental* to it as are the hemorrhagic erosions.

a. Psychogenic Ulcer. This group alone is in the author's opinion the cause of about 95% of all gastro-

*We wish to emphasize the extreme importance of this conclusion. There would be a great saving in morbidity and mortality if that thesis were more generally taught instead of the prevalent one that urges surgical intervention on any patient over 40 who has a benign ulcer.

duodenal lesions. It is the common chronic ulcer generally designated as "peptic." Earlier in this paper reasons were given for discontinuing the use of this word. Instead the word "psychogenic" seems more correct etiologically speaking.

While there may be some difference of opinion as to whether the *psyche* alone can produce a gastro-duodenal ulcer, an ever-increasing number of clinicians agree that it plays some role. Dr. Ivy (14) says, "I have yet to meet a clinician of extensive experience who denies that sustained anxiety is a factor in determining the chronicity and recurrence of "peptic" ulcer in many cases." The literature is fairly replete with articles by outstanding men stressing the importance of the emotional factor in chronic ulcer. Current literature of the last few years contains more articles than during any previous period (15, 16, 17, 18, 11, 20). The following men have in their recent writings given expression to this view: Alvarez (37, 43), Alexander (19), Cannon (27, 28), Crohn (29, 46), Cushing (30), Draper (26, 2), Durante (22), Fulton (25, 44), Hartman (21), Mayo (24), Moschowitz (17), Russ (23), Rivers (38), etc.

The term "psychogenic" is gaining in popularity, and it has a specific connotation. The term chronic* if used alone is not descriptive, conveys no definite understanding of the type meant and is therefore insufficient. The looseness of the word "chronic" allows for the running together and confusion of ulcers belonging in separate groups. It is for this reason that classification in this field is essential. It would disentangle one type from another and assign each to its proper grouping in bold relief.

Let us see how applicable this becomes for the psychogenic ulcer. If we studied this single type of ulcer and recorded the findings peculiar to it we might gain a clear picture of the disease. A brief summary of such findings would be as follows: The history is one of years' standing and is unusually constant and classic. Distress comes one to two hours after meals and is relieved by food. There are seasonal remissions and exacerbations. As yet the psychogenic ulcer has not been found in the lower animals, rarely in the *pure* Negro, occurs most frequently in the long thin white person, at least ninety-five out of one hundred; occurs in the male about eight to twelve times as frequently as in the female; occurs in certain personality types with a fairly definite pattern of emotional instability. It is associated with hypermotility of the gastro-duodenum, hyperchlohydria, and hyperacidity. The location of the ulcer is along the lesser curvature of the stomach and the first portion of the duodenum. The pathology shows a clean cut-out ulcer with adjoining mucosa normal,* (31) with thrombosis, ischemia and induration. The kidney function is normal, the blood pressure is normal and the blood picture is normal (11). There is a growing recognition that the foregoing constitute the "irreducible minimum" of the findings in the largest percentage of psychogenic ulcers, in which case the elucidation of this disease becomes greatly simplified.

Any theory of etiology would have to fit these divergent and widely separated findings into a complete mosaic. Contrariwise, the presence of so many different findings common to this unique disease limits the number of possible hypotheses that can be advanced. For instance, the theory of focal infection could not stand up very long to explain all the facts surrounding the disease. The *pure* Negro is as subject to focal infection as the white race if not more so, yet the race on the whole rarely develops the disease. Likewise the "lateral" type individual should have as many infected teeth, tonsils, prostate, gall bladder, appendix, endocardium, dura, et cetera, as the long thin type yet he seldom develops an ulcer. The female ought to have as many bacteria floating in her blood stream seeking a place upon which to alight as the male yet only one of her sex develops an ulcer to ten of the males. We need not go any further to show that the application of logic alone in this one matter of focal infection* would settle the question in the negative without much ado if most gastro-enterologists accepted the findings in connection with the gastro-duodenal ulcer as stated above.

But a large percentage of the findings unfortunately are not generally accepted and in a certain measure because of errors in classification. Let us consider ways in which the findings of a psychogenic ulcer could be confused easily with some other type and thus *vitiate the value of the true picture in each case.*

b. Hemorrhagic Erosions. These erosions occur in connection with many acute or chronic diseases, purpura, malignancy, nephritis, leukemia, gall bladder disease, and even as post-mortem changes. These are the ulcers that most often are confused with the psychogenic type. The guess is ventured that the statistical findings in some series of the common chronic ulcer are made rich by what is seen in this group of hemorrhagic erosions.

Nephritis is responsible for the largest number of these gastro-intestinal erosions. Francine (45) found forty-two gastro-intestinal ulcers in a large autopsy series and seventeen of these were due to nephritis. These ulcers may occur in the esophogus, stomach, small and large bowel, but more frequently in the stomach.

There may be hemorrhage from *any* mucous membrane. There may be bleeding from the urinary bladder and from the mucous membrane of the upper respiratory tract, gums, pharynx and massive alveolar hemorrhage. In many instances the bleeding is due to diapedesis and no destruction of mucous membrane is visible. Dr. Jaffe reports one such case of fatal gastric hemorrhage and at autopsy no defect in the mucous membrane of the stomach could be found. But where the ulceration does take place it is fairly distinctive. The ulcers are very shallow, show no evidence of induration either at the margins or at the base, *i.e. the* underlying structures seem unchanged. The whole wall is soft to the touch, the process appears of recent origin, days or weeks, as if a very thin

*The acute and chronic ulcer are identical in etiology and differ only in most instances in the time-interval of observation. Out of a hundred supposedly acute gastro-intestinal ulcers, if observed over a five year period, approximately 90% of them would show exacerbations of the ulcer syndrome if not of the actual ulceration. In this paper, therefore, the term "chronic" will be used to include the so-called acute group.

*"In my gastroscopic observations, in at least one-half of the gastric ulcers, I found the surrounding *mucosa normal*. No infection or swelling was visible."

*This does not constitute the entire argument against the *rôle* of focal infection as a major factor in the etiology of gastro-duodenal ulceration. The reasons presented have been limited to these few relevant facts to demonstrate the value of classification and the orderly grouping of findings in unravelling the mysteries of this disease.

layer of the superficial mucosa were sliced off. These ulcers may be very large. The adjoining region may be hemorrhagic and the whole gastric mucosa may show hyperemia. The ulcers may occur anywhere in the stomach, as often on the posterior aspect as on the lesser curvature. The average pathologist would recognize such as an atypical ulcer not belonging to the common and classic gastro-duodenal type of ulceration which occurs on the lesser curvature with induration and thrombosis. Yet the anatomical diagnosis of these nephritic ulcers would read as follows: 1. "Nephritis. 2. Hypertension. 3. Peptic ulcer," and unless one recognized the proper group into which this ulcer belongs one would record in the permanent literature a psychogenic (chronic) ulcer associated with hypertension and nephritis. Only in a very narrow sense is this true, surely in no way to throw light on its real etiology.

The patient suffered with nephritis and hypertension for years and gave little sign of gastro-intestinal upset. As a terminal and probably toxic development in the long course of his illness he developed an erosion of the stomach. This gastric lesion is as incidental to nephritis as a bed sore is to any patient with a long bed-confining illness, and has as much reversible relationship. The ulcer in the gastro-intestinal, respiratory or urinary tracts played no major *rôle* in the disease itself, at least not so far as the underlying pathogenesis of nephritis is concerned. It may hasten the death of the patient through internal hemorrhage but this is accidental and not relevant to the disease or its elucidation. Similarly, a patient with Raynaud's disease may develope lymphangitis in one of the phalangeal ulcerations and die therefrom. But the lymphangitis would have had nothing to do with the etiology of Raynaud's disease. Is it possible that the great discrepancy in the incidence of hypertension in the psychogenic (chronic gastro-intestinal) ulcers is due to such an error? The actual percentage as given by different authorities varies from 2% to 14%. This is entirely too great a difference in so clear-cut a disease of a finding so easily determinable. This is not a mere academic issue for two reasons. In the first place, many men claim that hypertension plays a *rôle* in the etiology of psychogenic ulcer.* Secondly, those of us who claim it is a neurocirculatory disease are keenly interested in interpreting the mechanism of the autonomic system that limits its vascular constricting effects to the stomach and duodenum and spares the peripheral vascular bed.

We may now cite a reported case in the literature which illustrates the point first mentioned, namely, the danger of attributing to psychogenic ulcer specific findings that in reality belong to other types of gastro-duodenal ulceration.

Case I. Colored male, 41 years of age, ill for 8 months with shortness of breath, nausea, vomiting and indefinite soreness in abdomen. There was a marked loss of weight and swelling of ankles. History of a chancre and of gonorrhea. BP 160 60. Heart was enlarged, and there were systolic and diastolic bruits. Both lung bases showed impaired resonance and rales; the liver was enlarged. *At autopsy*, at the Cook County Hospital in Chicago, Dr. Jaffe found multiple ulcers on the greater curvature "irregular in shape and atypical in location—deep with soft edges and apparently of short duration and their multiplicity and irregularity indicate that they developed from hemorrhagic erosions." The anatomical diagnosis gave no clue of any specific disease (32).

This patient obviously did not belong to the psychogenic type of ulcer. Dr. Jaffe, the pathologist, was quick to recognize this and to mention its atypical characteristics and its different etiology as due to hemorrhagic erosions. The findings if *loosely* grouped would be incorrectly classified as those of a psychogenic ulcer showing the following five points: 1. The ulcer occurred in a Negro. 2. Occurred along the greater curvature. 3. Was associated with hypertension. 4. An organic murmur was present. 5. The histopathology showed: a. Multiple ulcers. b. Soft edges and no induration.

The inclusion of these findings as typical of a patient with psychogenic ulcer would be incorrect statistical evidence. *Not one of these findings is ordinarily associated with a psychogenic ulcer.* It is not common in the Negro, does not occur along the greater curvature of the stomach, is not associated with hypertension or organic heart murmur: the ulcer is not generally multiple and its edges are not soft. The literature is full of these ulcers that are secondary to other diseases especially nephritis (9). These hemorrhagic erosions are often *bizarre* in their appearance and very atypical in their location. Some are very large as the following case demonstrates:

Case II. Reported by Crohn.

"The ulcer eroded nearly the entire posterior wall of the stomach so that the palm of the hand laid on it covered it with difficulty" (29).

The symptoms and signs of these ulcers must not be confused with those of the psychogenic type. Continued scrutiny would make the clinical picture of the psychogenic ulcer so clear and sharply outlined that etiological conclusions would force themselves upon us in logical sequence.

Another source of error in assigning wrong symptoms and signs to the psychogenic ulcer is an incorrect diagnosis. Smithies has called attention to this source of error and quotes William J. Mayo (33), "a patient may have been treated medically for a long time and yet the patient may have had no ulcer." Deaver (41), going still further and probably a little to the extreme says that not half the patients undergoing medical treatment for ulcer actually were subjects of ulcer.

It is also urged that the selection of the ulcer patient for statistical data be made from the younger age groups. Ulcer is a disease of youth and early middle life and the true picture should be sought here, rather than in advanced years when findings are contaminated by degenerative diseases.*

Even the X-ray is not infallible. Some defective duodenal bulbs that are diagnosed as ulcers are found to be something else at autopsy or at the operating table (33, 34).

c. Burns. These ulcers, often called "Curling ulcers" in honor of Curling (39) who described them in 1842 in a series of four of his own duodenal ulcers, may be found in cases after severe burns. They are most often found in the first portion of the duodenum

It is suggested that blood pressure readings be studied in a series of ulcer cases in which the age limit is from 35 to 45. If only the [illegible] type is selected, the incidence of hypertension [illegible]

*One must differentiate here between ulcer presence as diagnosed by the clinician and ulcer incidence as recorded by the surgeon or the pathologist. *Editor.*

as pointed out by Moynihan and since this is also the site of most psychogenic ulcers it was thought wise to make a separate group of them on the basis of this site selectivity. In most cases there is also to be found hemorrhage into the suprarenals and this relationship has offered interesting speculation. In the experimental animal partial destruction of the suprarenals results in duodenal and jejunal lesions in a fairly large percentage of cases (40).

d. Brain Trauma. Cushing in 1932 summarized the evidence of the production of gastro-duodenal ulcer following surgery, neoplasms and experimental irritation of the interbrain. Fulton, Watts, Hoff and Sheehan (35, 47), have demonstrated that gastric erosion may be produced following experimental lesions of the hypothalamus in monkeys. This work is of the greatest significance not only in establishing the definite relationship between brain lesions and gastro-duodenal ulcers but also in establishing their most likely location in the diencephalon which is being looked upon more and more as the seat of emotions. It is this primitive brain which doubtless exercises most of the involuntary control of visceral function through autonomic control. Many pathways connect the diencephalon with the cerebrum.

e. Follicular Ulcer. This is a very rare ulcer occurring chiefly in infants. It involves the lymphoid tissue generally and particularly that of the stomach, and is probably on an infectious basis.

CONCLUSIONS

It is claimed that there has been considerable confusion of the different types of gastro-duodenal ulcers one with another. For clarification a classification of these various types of ulcers is presented. A major division is made into "Direct" and "Indirect" causes. The *Direct* ulcers constitute but a small proportion of all gastro-duodenal lesions and includes those which have their origin in the wall of the stomach or duodenum. The *Indirect* group, comprising by far the largest number of ulcers seen, includes those whose causes, such as psychic, toxic, bacterial, etc., come from outside the gastro-duodenal wall. They may be the primary manifestation of a systemic condition as in the case of psychogenic ulcer, or they may be very incidental to it as in the case of the hemorrhagic erosions. This latter group is the type most frequently confused with the true psychogenic ulcer. In order to have a clearer understanding of the psychogenic ulcer (chronic ulcer) so we may better be able to arrive at its etiology the factual data must be agreed upon. We have as yet not reached any unanimity of opinion about the objective data of chronic ulcer. Is there an ulcer type of individual—a "race" of white men that practically alone is susceptable to the disease?* Is there a definite constitutional build and personality type amongst these patients? Is the pathology of the ulcer distinctive? Is it different from other ulcers in the gastro-intestinal tract? These questions strike at the very root of the whole ulcer problem. Our knowledge of any disease entity is built up painstakingly by recording the subjective and objective findings associated with it. We then try to assign some causative factor that would duplicate these findings. If our objective data are in error our interpretation of them in light of etiology must be faulty.

If we were to assign correct findings to the proper ulcer types we should then have no difficulty in establishing the clear cut and true picture of the psychogenic ulcer patient. It is claimed that the following would constitute the *"irreducible minimum"* findings in by far the largest per cent of cases: The history is of years' standing, of seasonal exacerbations and remissions, the classic story is upper abdominal distress after food which in turn is relieved by food. The build of the patient in over 95% of the cases is long and thin. There are ten times as many males as females. There is a definite personality pattern of emotional instability associated with worry and fear. The histopathology is a sharply cut out and clean ulcer occurring in the first portion of the duodenum and along the lesser curvature. The adjoining mucosa is normal, with thrombosis and induration with maximum involvement near the serosa. The X-ray shows hypertonicity of stomach and duodenum. There is hyperacidity. Nearly all the other findings are normal including blood pressure.

If we agreed upon these findings the etiology would become much more apparent.

SUMMARY

1. A classification of gastro-duodenal ulcers on an etiological and clinical basis is presented.

2. There is discussion of the limitations of histopathology in the elucidation of the chronic ulcer and other psychogenic diseases. For that reason the pathological picture of the ulcer itself plays a minor role in this classification.

3. Evidence is advanced to show the inadequacy of the term "peptic" as descriptive of gastro-duodenal ulcers. The term "chronic" is shown to be loose and without any specific connotation.

4. The term "psychogenic" is suggested as a substitute because it is descriptive of the causal relationship of the disease.

5. Malignant transformation does not occur in a benign psychogenic ulcer.

6. Traumatic ulcer is classified as brought about by direct causes and therefore could not result in a psychogenic (chronic) ulcer.

7. The subjective, physical and laboratory findings of hemorrhagic erosions should not be included in statistical studies of the psychogenic type of ulcer.

*In a comparative study of disease, morphology and emotional response of the Negro race in the U. S., the most deeply pigmented members should be selected for any adequate approach to true racial representation. Mulattoes, quadroons and octoroons do not represent the Negro.

There is full anthropological and social evidence to show that the Negro is a more primitive member of the human race. A good summary is "Human History," by G. Elliot Smith.

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New Experiences with Simmonds' Disease

By

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TEN or twelve years ago Simmonds' disease was very rarely mentioned in medical literature. Latterly, however, articles on this subject have appeared more frequently, particularly in German, French and English publications. In German literature the works of the Hamburg researcher Reye helped very largely to propagate popular knowledge as to the nature of this disease. Since then, however, many other authors (Grafe, Steinitz, Lightwitz, Redlich, Frazier, Wildner, etc.) have communicated similar cases. I myself have come in contact with two cases, a description of which has already been given, while in the last three years I have succeeded in discovering three recent cases which I should like to communicate here.

I. Woman, aged 61, had been ill for about a year. Main symptoms: intense itching and serious insomnia. Bodily strength markedly declining; loss of appetite, low spirits, suicidal tendencies. Had lost about 18 lbs. in weight in one year. According to previous medical opinion, the case was one of nervous debility; in hospital Addison's disease was suspected.

St. pr.: Face light brownish in color, with wrinkled withered skin and sad expression; great general debility; complete absence of hair in armpits. Moderate degree of anaemia. Roentgen investigation of stomach and intestines: negative. Thoracic organs sella turcica, blood sugar, blood pressure: normal. The increasing adynamia and apathy, lack of appetite, sleeplessness and the absence of hair in the armpits were signs that this was not a case of ordinary senile pruritus. For this reason I suspected a rudimentary form of Simmonds' disease and therefore prescribed hypophysis (anterior lobe) hormone. The effect was remarkable: after one week the patient already felt better, her muscular strength increased, and even walking did not trouble her.

The patient was under treatment for about 4 months. At first she was given 10 injections of the Prehormon preparation produced by the Promonta Factory and when the supply ran out I gave her temporarily, for lack of anything better and without her knowledge, injections of arsenic. After the third arsenic injection the patient asked me whether I should not have changed the treatment, for she again felt light-headed and walked unsteadily. After a short time she was again given Prolan per os and in the form of injections. When the supply of Prolan was exhausted, Richter's Glanduantin was administered and, after that, Horpan. The effect was excellent, while no difference was to be found between the various hormone preparations. After four months' treatment the

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Fig. 1. Case I—Before treatment.

patient was completely cured. Her weight had increased by over 17 lbs., her facial features were also altered and the skin looked fresh. The shedding had entirely ceased; whereas previously an X-ray treatment had to be given every six months, no irritation whatsoever has occurred for the past two years. The patient is completely fit for work; she is on her feet all day and does her work perfectly. It was not easy to make a diagnosis in this case. While local symptoms were completely absent, the development of prepotent general cachexia permitted the deduction that Simmonds' disease might possibly be present. The success of the specific treatment confirmed the diagnosis in every respect (Figs. 1 and 2).

II. Girl, aged 20. Able to walk only when supported by two persons. The mother stated that the patient had had no appetite for about nine months and was losing weight. The parents believed that as the result of a psychic trauma their daughter had lost the desire to live. She never had fever. Disordered sleep; examination of the bowels only after taking a purgative.

St. pr.: Greatly emaciated; height 5 ft. 7 in., weight 73 lbs., heavily-built (normal weight 121 lbs). Skin pale and flaccid, tongue slightly coated, eyes glazed. The skull when examined by touch and also when X-rayed was found to be normal. Heart, lungs, aorta, diaphragm: normal. Stomach normally curved and ptotic. Peristalsis was rather weak, gastric digestion took about 5 hours, the duodenum was quite normal. After 24 hours the colon was completely filled by the contrast clyster. The transverse colon was highly ptotic, the cecum normal; the skiagrams of the kidney and suprarenal capsule showed no calcified areas (Addison). No parasite or concealed haemorrhage was to be found in the stools; urine and blood pressure were normal. Blood sugar 130, Sahli 75, number of erythrocytes 3,000,000, leucocytes 6,700, normally distributed; blood gravitation velocity normal. No pathological changes were observed in the sensory organs or in the nervous system; sight, hearing and reflexes good.

In view of the disparity between the local and general symptoms I thought it might be a case of endocrine cachexia, especially of Simmonds' or Addison's disease. The relatively large amount of blood sugar was opposed to Addison's disease, although in Simmonds' disease also the quantity of blood sugar is usually low. A high blood-sugar factor, however, tends to disprove the presence of Addison's disease. As a precautionary measure I administered both Prolan and Cortigen, for whichever of these diseases was present one of these two remedies would have to take effect. The efficacy of Richter's Cortigen in saving life I had already proved in the case of one of my patients suffering from Addison's disease—a case which I described in the American Journal "Endocrinology" (1931). The excellent effect of Prolan was known to me not only from the literature concerned but also from personal observation. After eight days I discontinued the administration of Cortigen. In addition to the blood-sugar factor, the patient's apathetic attitude also indicated that this was more likely to be a case of Simmonds' disease. For another three weeks the patient continued to lose weight. Then the wasting process was checked, and in the fourth week a slight increase in bodily weight was recorded. After two months' treatment the patient was discharged, by which time her weight had increased by nearly 8 lbs. Meanwhile her strength visibly increased, her appetite improved, she slept well and was already able to walk without assistance. The face filled out, the skin lost its previous alabaster pallor, vitality and enjoyment returned. For a considerable time still the hormone treatment was continued at home by the family doctor, and then definitely stopped. One year later the patient was so strong and healthy that she was chosen as representative by a sports association of her home town—a distinction which is rarely accorded to persons suffering from Simmonds' disease (Figs. 3, 4 and 5).

III. Man, aged 45. Had been ill for three years, and during the previous seven months had become markedly weak and pale, while losing appetite and weight. During the same period he had become hard of hearing in the left ear. Most of the symptoms were associated with the stomach: gastric oppression and a feeling of fullness, also occasionally pain. Marked perspiration ½-1 hour after food. Was totally unfit for work; impotency had appeared about six months previously.

St. pr.: Pallid skin, tired expression, hollow-eyed; slow movements like those of an old man. Hair on scalp and body normal, tongue slightly coated, tonsils normal, pupils reacted promptly to light and accommodation. Blood pressure according to Riva-Rocci's test 90. Results of X-ray examination: heart normal, aorta regular. On medial right, below the clavicle, a primary complex of the size of a pea. In the apex of both lungs small calcified patches hardly as big as a lentil. Diaphragm free, stomach normally curved, its position and size normal; increased peristalsis, loiliew of usual shape, remaining portions of



Fig. 2. Case I—After treatment.



Fig. 3. Case II—Cachexia high grade—Before treatment.

duodenum also normal. Evacuation normal, the stomach empty in five hours, the small intestine filled, the colon showing incipient filling. After seven hours, the position was unchanged. After 24 hours the filling had reached only the middle of the transverse colon. The cause of the delay was the caecum ascendens, situated far down in the true pelvis. By means of X-rays and a contrast clyster it was possible to observe clearly the colon throughout its length, and it proved to be normal. Test breakfast results: free hydrochloric acid 20, total acidity 40, blood negative. The skiagram of the suprarenal capsules showed no abnormal, calcified patches. Wassermann reaction negative, blood sugar 123. Blood picture: number of erythrocytes 3,900,000, leucocytes 7,000, Sahli's test 75; rod-nuclear cells 3%, segmented 72%, lymphocytes 24%, monocytes 1%. The patient was given Preloban per os, as also Prolan and Cortigen in the form of injections. In two days the effect was already apparent. The patient felt stronger and was better able to walk, his bearing became more confident and his appetite returned. In the first week he gained over 3 lbs. Moveover, the improvement has been continuous, the increase in bodily weight being now about 10 lbs. (Figs. 6 and 7).

What is the real nature of this disease? A hypofunction of the anterior lobe of the hypophysis? It may or may not be accompanied by morphological changes. Reye observed Simmonds' disease in women only, and among my own patients there were four women and only one man. Reye considers that Simmonds' disease is present only in cases where an idiopathic primary change has occurred in the anterior lobe and not in those where this lobe is being destroyed by syphilitic gummata, a tubercle, a tumor or meningitis. He is of the opinion that the idiopathic decay of the specific tissue is the essence of Simmonds' disease. This conception, therefore, visualizes a change in the anterior lobe such as that observed in the liver in cases of cirrhosis, in the kidneys in cases of chronic nephritis, and in the heart when myofibrosis is present. According to Reye, there are also lighter cases in which only a part of the gland tissue is diseased. This is highly probable, for the patients usually recover after a 2-3 months' treatment and keep well even when they receive no further treatment perhaps for years. This can only be attributed to the fact that the endogenous hormone production has begun anew.

In the symptomatology of this disease many symptoms have been described, but, unfortunately, these are not always reliable guides. It would hardly be possible to find a symptom which could only be attributed to disease of the anterior lobe of the pituitary body. From the variety of symptoms one may diagnose now a thyroid or suprarenal disorder, now a derangement of the genital glands. How may these ailments be differentiated? A myxoedematous patient is fat, or at least does not lose weight, whereas a person suffering from Simmonds' disease loses weight continuously and the flesh may waste away down to the very bone. The tongue of the former is thick, while that of the latter is normal or thin. The best method of differentiation, however, is *ex juvantibus*. A person suffering from Simmonds' disease, however myxoedematous he may appear, is not restored to health by thyroid hormone, but is easily cured by hypophysis hormone. Menstruation ceases early, owing—as we have learned from Zondek's investigations—to diminution in the formation of the gonadotropic hormone. Individual symptoms, such as falling out of hair and teeth, drowsiness, amenorrhoea, emaciation, apathy, pallor, have no special significance as they may also be due to disease of other glands. Lack of appetite, vomiting, adynamia and pain in the gastric region occur mainly in Addison's disease. It would be much more useful if exact hormone analyses could be prepared, and if it could be mathematically established how many units of each hormone were lacking. As things are, the individual imagination has a wide field. I am, however, decidedly against the administration of insulin, having observed only bad results therefrom, while I share Lucke's opinion as to the extreme sensitiveness to insulin of persons suffering from Simmonds' disease. The hypoglycaemia of the patient cannot tolerate any further reduction by means of insulin. In such cases it does no good, but only harm.

So far I have observed no case which resisted treatment by hypophysis pars ante. hormone, but I do not



Fig. 4. Case II—After treatment.

dispute the possibility of such resistance. We must not forget, however, that it has been possible to arouse from diabetic coma patients who had already been given up by giving them 1,000-1,500 units of insulin, instead of the otherwise usual 100-200 units. Perhaps the patients' resistance to this treatment was due to the fact that the preparations formerly used were not sufficiently concentrated. Naturally, even a hormone treatment cannot cure the patient if a tumor is pressing upon the anterior lobe, or if a metastasis occurs in the lobe.

Falta used to refer to primary anorexia, while Bergmann speaks of "absent appetite" (Aehlender Nahrungstrieb). What is the cause of this symptom? The same as that of low blood sugar, emaciation and low



Fig. 5. Case II—One year after treatment.

bodily temperature. The patient is not suffering from Simmonds' disease because he has no appetite; his lack of appetite is due to the tissues being unable to use the energy supplied. The lack of appetite is, as it were, a semaphore which is set at "Stop" for food. Bergmann frequently emphasizes the significance of *disorders in the gastric region*. The majority of the patients do in fact complain of such disorder. My first patient vomited continually, and was under the impression that the oculist who was treating her at the time had dropped something poisonous into her eyes. My last patient had also gastric trouble and complained of oppression and a feeling of fullness, vomiting and an unpleasant, but otherwise undefinable, weakness. Many doctors would be inclined to advise an operation in such cases, and it is probable that for this reason laparotomy is sometimes performed without any need, as Bergmann correctly states. To guard against such unpleasant mistakes there is only one remedy: a reliable and thorough X-ray examination. In cases where an elderly, carcinomatous-looking patient "forgets" to die, or where an apparently tuberculous patient is found to have normal lungs, Simmonds' disease should be suspected. An important symptom is the *decline in basal metabolism*, although it is at present difficult for the general practitioner to establish such diminution, while opinions as to the Read formula are still divided. Kestner considers the absence of the *specific dynamic action* to be a highly important symptom. I myself have no experience in this field.

Cases of serious gastric disorders in which the X-ray and chemical examinations have given negative results lead one to suspect some endocrine derangement. Such cases are most likely to come under the notice of clinicians who are at the same time radiologists. While the radiologist can gather nothing from negative results, the clinician will find therein a valuable guide. Bergmann attributes the gastric trouble to the hypophysis, which plays an important part in the digestive tract; he holds the view that the posterior lobe is also affected. In my opinion gastric disorders are not due to a diminished function of the posterior lobe of the hypophysis but to a decreased activity of the suprarenal bodies, and such disorders respond rapidly to cortical hormone, as also to hypophysis (anterior lobe) hormone. Kalk obtained good results by giving his patients grape sugar, without insulin. Although this may be useful as a therapeutic adjuvant, it certainly cannot replace the hormone treatment.

Experience teaches that the diagnosis of Simmonds' disease is very difficult. No diagnostic skill, no reading, however wide, can avert the danger of failing to recognize the disease. In two very serious cases there were, so to speak, no symptoms. This observation was also made by Reiche, for which reason he refers to rudimentary and atypic forms of disease. A serious illness may be developed without a single symptom affording guidance. Moreover, no symptom is a trustworthy guide, for each may be caused by a different gland. *The most reliable indication is the curative action of the specific hormone*; the "ex juvantibus," which is, in view of the excellent and concentrated preparation now obtainable, the most valuable and the most reliable guide. A precise diagnosis of the malady is in future to be expected only from a reliable hormone investigation. I am at present occupied with a diagnostic test in this connection, and hope to be able soon to begin the necessary work. My ideas run on the following lines:

A pregnant woman secretes quantities of gonadotropic hormone. In the pregnant woman there is a sufficiency of hormone, in a person suffering from Simmonds' disease there is a deficiency. If I now give a normal person an injection of hormone in the same quantity as that secreted on the average by a pregnant woman, the excess amount will be discharged from the body in the urine. If I give the same quantity to a person suffering from Simmonds' disease, it is not discharged because the hormone is fixed by the hormone-starved organism. Thus, while in a normal organism the Zondek reaction occurs after x hormone units have been injected, is this reaction absent in a sufferer from Simmonds' disease? The difference between the two quantities of hormone given to the two persons by injection shows the extent of the patient's hormone insufficiency.

A counter test to this would be as follows: The "Simmonds" patient is given an injection of hormone in such a quantity that his urine shows the Zondek

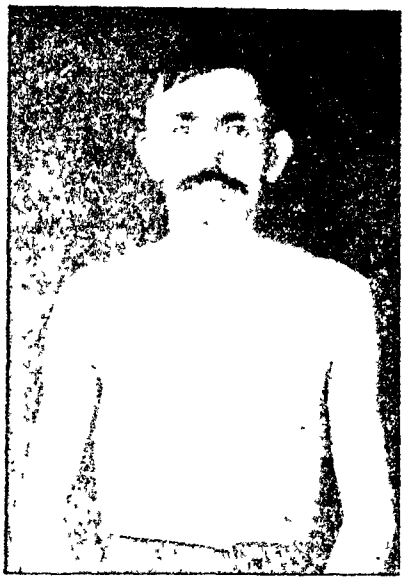


Fig. 6. Case III—Before treatment.

reaction. For this purpose a considerably larger quantity of hormone will be required than in the case of a normal person. From the amount of hormone administered the patient's hormone-producing capacity may be deduced; in healthy persons it will certainly be different from that of sufferers from Simmonds' disease. The purpose of this test would be to provide quantitative figures for the diagnosis of Simmonds' disease. This figure will be more or less constant in the case of healthy persons; in sick persons, however, it will vary. In cases where considerably more hormone units are required to induce the Zondek reaction, a hypofunction of the anterior lobe is present. This will enable a more exact diagnosis of Simmonds' disease to be made than heretofore.

Whether this conception will or will not prove useful in practice, only the future can show.

Another interesting question is: Why does coma never supervene in Simmonds' disease? It occurs in diabetes, in Addison's disease, and even in exophthalmic goitre. The cause may be found in the following facts: The disease itself is chronic, its course is slow and without any acute shocks. The organism does not lose strength suddenly, but only very gradually. Another cause may be that the ratio of the three main sources of energy—albumins, carbohydrates and fat—remains the same during the illness as in health. There is a general diminution, but not a disproportionate one. Here there is no deficiency of carbohydrate as in diabetes, nor any derangement of albumin metabolism as in exopthalmic goitre. Perhaps it is the existence of the normal ratio—even though on a greatly reduced scale—that safeguards the patient from the sudden occurrence of toxic symptoms.

Now the further question arises: which hormone is really contained in the well-known preparations Glanduantin, Prolan, Horpan, and Prehormon? As far as we know, it is the gonadotropic hormone. This is, however, contradicted by the action of these preparations whereby metabolism is markedly improved. What follows from all this? Either the much-discussed metabolic hormone does not exist or it is identical with the gonadoptropic hormone, or else both are contained in the preparations now on the market. In my patients, as regards the genital glands, I observed either no improvement at all or only a very slow one—in elderly persons this is, of course, readily understandable.

On the other hand, a marked improvement in the patients' metabolism invariably occurred. The fact is, therefore, clinically important: that I have always observed a remarkable improvement in metabolism as the result of gonadotropic hormone.

It is also gratifying to note that the *therapy of the disease* has progressed. In his earlier articles, Reye already emphasized the good results obtained by administering hypophysis fresh from the slaughterhouse. Since then research work has made great progress, while science has enriched us with excellent remedies, which are deserving of the highest praise. *Most of my experience has been with Richter's Glanduantin*, which I consider to be a means of saving life in cases of Simmonds' disease. Its action is equally reliable here as that of insulin in diabetes, with this great difference: that in 2-3 months the patients have so far regained their strength that no more hormone is needed. Glanduantin is not a substitution remedy but a real cure. I have had similar results with Prolan and Preloban; also of Pregnyl, a Dutch preparation, Horpan, a Dresden preparation, and Prehormon, a product of the Promonta Factory, I have nothing but good to report. With these preparations the physician can obtain amazing results. I am already inclined to believe that in view of these excellent and highly concentrated preparations (ampoules with 500 units are already obtainable), the dosage of which can be accurately determined, no single sufferer from Simmonds' disease need die of it, provided the doctor is able to recognize the malady. When we consider what successful work has been achieved by Simmonds, the gifted pathological anatomist, of Hamburg, Reye, the distinguished Hamburg clinician, and Bernard Zondek, the world-famous hormone student and gynaecologist, it is difficult to refrain from declaring

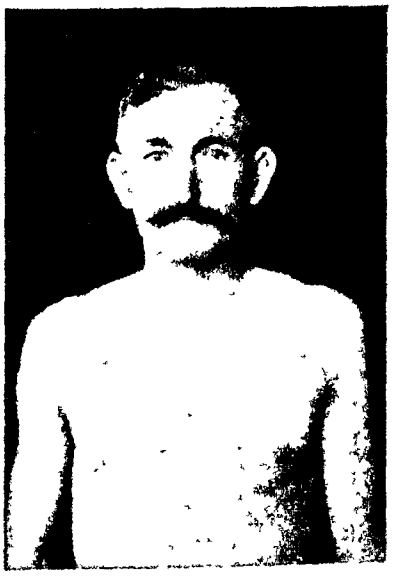


Fig. 7. Case III—After treatment.

emphatically that these men are among the greatest benefactors of mankind.

As regards the dosage, no fixed rules can be laid down. It is impossible to say whether 100 or 200-300 units a day will be required. It depends entirely on the individual. I had patients who felt well when taking 100 units a day and others when taking 700 (seven hundred) units a day. The proper daily dose for the patient is that quantity of hormone on which he gains weight. It varies greatly. Sometimes the increase in body weight begins late, but an improvement soon appears in the gastric symptoms, while the appetite and muscular strength increase; this improvement is accompanied by a subjective but, for the doctor, highly significant symptom: an amelioration of the patient's peculiarly unpleasant general feeling. "I don't feel so queer now" is a stereotyped saying of such patients. When these signs appear, the dosage is suitable. Whenever we are able to determine quantitatively from the urine the insufficiency or any improvement in the separation of the hormone, then we shall also be able to prescribe the dosage with mathematical precision. For the time being, it is important to note that even the present therapy is successful and represents one of the greatest achievements of medical research.

I will not venture to say that the correction of the pathological process is effected by the hypophysis hormone alone. Moreover, we do not know how and in what manner it acts. It is possible that the mere presence of the hormone is sufficient; perhaps it regulates the activity of the neighbouring large vegetative centres. In his excellent book, Raynaud speaks of "signes d'emprunt," i.e. of symptoms which are "borrowed" from the neighbouring vegetative centres, but it may be possible that the vitamins also play some part in the process—a theory which I consider highly probable. References to a connection between the vitamines A, C, D and E and the hypophysis are appearing with increasing frequency in medical literature (Verzár, Vogt, Moravitz, Abderhalden, Kühnau). Possibly, the hormone stimulates some process which paves the way for the necessary vitamin or perhaps neutralizes the effect of an opposite vitamin. In the cogwheel-like arrangement of the endocrine system it may easily be that the failure of one factor impedes the other factors. However that may be, one thing is certain: that the anterior lobe hormone plays a dominant part in the treatment of Simmonds' disease, irrespective of whether the action takes place directly or indirectly. Further research will throw light on the intricacies of the working mechanism.

Value of a Routine Red Cell Sedimentation Test in Gastro-enterology*

By

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PATIENTS attending a clinic for gastro-intestinal disorders usually complain of symptoms referable to the digestive system. Investigation however, often shows that the cause of the symptoms lies, not only outside the gastro-intestinal tract, but frequently outside the abdomen altogether. Aware of this, the gastro-enterologist must not let himself be misled by the patient's concentration upon digestive manifestations. He must rather, look beyond his own specialty, considering the patient as a human being—not as a mere digesting mechanism.

Therefore, the red cell sedimentation test as applied in the broader field of general medicine, including ailments remote from the digestive tract, may very well become a valuable aid in gastro-enterological diagnosis. Even though a negative finding with the red cell sedimentation test does not positively exclude the existence of disease, the value of a *positive* sedimentation is in no wise lessened. When this is the only evidence of disease it may well excite the examiner to greater care, and has in many instances thus enabled wholly unsuspected pathological states to be made manifest. Thus its employment in a gastro-intestinal clinic, where cases of both types are continually encountered, will be as beneficial and helpful as this test has long since proved itself in clinics devoted to gynecology or the control of tuberculosis.

Many authors have shown how closely related are the affections of the female genital tract and the gastro-intestinal system, while the relations which any type of tuberculous infection will establish with both these systems is too well understood to need more than passing mention. Runyeon (1) has illustrated this in the instance of the Krukenberg tumor, while Friedenwald and Morrison (2) have made an elaborate analysis of the reciprocal relationship between gastro-intestinal disturbances and pathologic conditions in the female pelvic cavity. It has been clearly demonstrated that such a test has practical clinical application in many conditions wherein it has not up to the present time, been used.

THE TEST

What we have here termed the *red cell sedimentation test* is known by a number of different designations. Since its introduction by Fahreus (3) in 1918 it has been called simply "the sedimentation reaction," or been known as

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'the suspension stability reaction of the erythrocyte,' 'rapid cell sinking' or 'rapid cell settling,' or again as the 'acceleration of sedimentation velocity.' All these refer to precisely the same phenomenon, which may be briefly described as follows:

Sinking of the red blood corpuscles takes place in the *presence of an anticoagulant, leaving a clear plasma.* This sinking is more rapid when disease is present, than when the body is healthy. This test appears to be the acme of simplicity, but it must be emphasized that its proper interpretation is not the function of the laboratory technician, but must be made by the clinician himself, as he alone is able to translate the findings in terms of all the other factors essential to recognition of disease in the body of the patient whose blood gave positive findings to the test.

The cell *sedimentation rate* is distinctly separate from the sedimentation *time*. For the time is inversely proportional to the severity of the disease; i.e. when the rate is increased, the time is lessened. The phenomena most significant for the test occur during the first hour. Beyond that period very little information of value can be obtained. Of the many hypotheses advanced to account for these phenomena, that most generally accepted is that in the presence of disease there is increased tissue destruction and the liberation of fibrinogen in the blood stream, with ensuing clumping of the cells. The larger the clumps, the more quickly will they sink.

INTERPRETATION OF THE TEST

Charting the sedimentation values in different types of cases, Cutler (4) obtained four graphs which he names horizontal line, diagonal line, diagonal curve, and vertical line. "Of these," he writes, "the horizontal line alone is normal. The other three graphs are always abnormal findings and always indicate different degrees of the intensity of the destructive process." "Its chief value," remarks Haskins (5), "is not in differential diagnosis but in following the course of the individual case, and in giving a clue to unsuspected infection, inflammation or malignancy in persons in whom a normal rate has been expected." In much the same strain Bannick (6) calls attention to three general principles: (1) An increased sedimentation rate always indicates the presence of disease of some kind; (2) but a normal rate does not exclude the presence of disease. (3) The rapidity of sedimentation is a measure of the severity of the disease, and when a level has been established in a given case, the rapidity of sedimentation provides a measure of the progress of the disease in that case.

That apprehension on the part of the patient may be a factor in erroneous readings of the test, is pointed out by Van Antwerp (7). To obviate this chance of error, he performs two sedimentation tests on successive days upon all newly-admitted patients. The lower of the two readings is accepted as reflecting the presence or absence of a destructive lesion.

VALUE OF THE TEST IN PEPTIC ULCER AND CANCER

A reliable means of differentiating between malignant and benign lesions of the digestive tract has long been sought by gastro-enterologists without avail. Does the red cell sedimentation test fill this need? Rubin (8) avers that in its early stages cancer does not necessarily induce an increased sedimentation rate, and cites a case of carcinoma of the esophagus, wherein the patient, otherwise in good physical condition, had a normal rate. Eleven months after the test was made the patient was returned to the hospital, and died shortly after of cancer, thus demonstrating that the sedimentation test may be unreliable when malignancy is in a very early stage.

As regards peptic ulcer, or its differentation from gastric cancer, Rubin, writing in collaboration with Morriss (9), and later (10), makes several citations from literature tending to indicate that the sedimentation test is of diagnostic aid when ulcer must be differentiated from cancer of the stomach, as cell settling has been shown to occur more rapidly if the lesion is malignant. Our own findings, in a comparatively small series of cases, tends to confirm the views which Rubin quotes. We agree with Held and Goldbloom (11) who found that though the sedimentation

Abstract of one hundred gastro-enterological cases and control study of twenty-two normal senior medical students

Disease	No. Cases M	No. Cases F	Low — High M	Low — High F	Average M	Average F	Remarks
Neurosis	17	9	2-13	4-13	5.05	8.07	In these cases, normal sedimentation rates, with negative physical findings led to the diagnosis of functional disturbance.
Chronic gall bladder disease	2	9	25-26	14-24	25.5	19.8	Clinically, the rate parallels the activity of the disease.
Calcified gall bladder		1		4		4	In this single case the low rate showed the disease process to be inactive, indicating an environment unfitted for microbic activity.
Duodenal ulcer I. Without bleeding or obstruction	6	2	2-14	14-14	6.8	14	The test here gauges the activity of the lesion, with bleeding as the main feature. In one case, the active ulcer showed 37 mm., but only 7 mm. in the latent period. Hemoglobin index rose as sedimentation rate fell. Lesions of the posterior duodenal wall bled more, and therefore show a more rapid sedimentation rate than those on the anterior wall.
II Bleeding, with and without obstruction	7	2	15-37	16.5—19.5	23.2	18	
Carcinoma of gastro-intestinal tract	4	3	15-37	26-28	24.8	26.3	In differentiating between benign and malignant gastric ulcer, if a high sedimentation rate is obtained in the presence of bleeding, it is not so indicative of malignancy as a high rate when bleeding is not conspicuous. Rapid sedimentation may occur independently—before characteristic symptoms appear. Rapidity of rate apparently parallels advance of the disease process.
Benign achylia gastrica	2	6	3-4	2.5—7.5	3.5	5	In true achylia gastrica the sedimentation test differentiates between benign and malignant types, a high rate usually indicating malignancy.

Miscellaneous Cases. Too Few to Permit Conclusions to be Drawn From Them. (Rapid red cell sedimentation fixes attention, leading to further observation and repeated testing to reveal the lesion; normal rate of sedimentation, correlated with other negative factors, justifies the assumption that disease is not present)

Disease	Number of Cases	Rate in MM.	Remarks
Acute retrocecal appendicitis	1	25	This case presented the classic symptoms of cholelithiasis; the white count showed a polymorphonuclear leukocytosis, with a marked shift to the left. Gall bladder normal cholocystographicly.
Acute suppurative appendicitis	1	30	Clinically unusually quiescent, operation in this case revealed appendiceal suppuration.
Vague gastric disturbances; metrorrhagia	1	23	Nullipara, 40, no miscarriages; husband's blood Wassermann repeatedly negative; own Wassermann, 4-plus. Vague symptoms of indigestion; diplopia following influenza; no clinical lesion demonstrable. Patients with positive Wassermanns but showing a normal sedimentation, appear to have latent syphilis. The test, therefore, differentiates between latent and clinically active syphilis.
Dental sepsis; gastric disturbance	1	7	
Irritable colon	2	11	
Lamblia duodenitis	1	23	
Glenard's disease	3	6-15	
Gastric hyperacidity	5	4-16	
Deferred diagnosis	7	3-25	
Gastric hyperacidity	6	4-16	
Umbilical hernia; hyperchlorhydria	1	8.5	
Tuberculous pleurisy	1	23	
Neurosyphilis	1	12	
Syphilis	1	Norm.-7	
Amebic ulcerative colitis	1	30	
Non-specific ulcerative colitis	1	23	
Periodic health examination	1	15	
Neurogenic diarrhea	1	4	
Diverticulosis; diverticulitis	1	27	
Gastro-enterogenous diarrhea; cholecystectomy; infection	1	17	
Acne and vague gastric disturbances	2	13-16	
Graves' disease	1	7	
Nutritional anemia	1	15	
Erythremia (persistent polycythemia or Vaquez's disease)	1	0	
Migraine of biliary (?) origin	1	21	
Cardiospasm	1	15	
Non-infectious granuloma abdominis	2	2-14	
Diabetes mellitis	1	19	
Major epilepsy	1	4	
Ulcer at pyloric end of stomach	1	12	
Pregnancy	1	19	
Roentgenologically diagnosed appendicitis	1	3	
Pyorrhea alveolaris; reversed peristalsis (Alvarez syndrome)	1	7	
Anxiety neurosis; (fear of appendicitis)	1	11	

Control Tests On Healthy Individuals

The normal controls were recruited from the senior class (1935) of the Homeopathic Medical College and Flower Hospital consisting of 22 male students. Only apparently healthy individuals, free from cold or any infectious conditions were asked to submit themselves to the test.

The following results were obtained:

Highest sedimentation rate	11 mm.
Lowest sedimentation rate	1 mm.
Average	4.3 mm.

All these readings are well within normal limits, and go to show, despite the very small numbers tested, that in individuals proved healthy after adequate physical examination, the sedimentation phenomenon will present a picture in no wise varying beyond normal limits.

rate was not increased in benign ulcer, when carcinomatous degeneration took place in such an ulcer, the rate was increased very regularly. All of our own cancer cases have shown a rapid erythrocyte sinking. We are therefore, of the opinion, that the red cell sedimentation test has distinct diagnostic value when striving to differentiate between ulcer and cancer of the gastro-intestinal tract. The findings of such authors as Barthold (12), who claims that the test is valueless in either extreme of the malady—the very early case or that which has advanced to the stage of cachexia—do not, in our opinion, find any application in the general run of cases seen in routine gastro-enterological practice. The results of investigations made by Lorie (13) several years ago, bear out our views. We would suggest that a gastric ulcer, in the presence of a low rate of settling, may be regarded as benign, if there is no associated gastris or duodenitis.

Relation of the Test to Hemoglobin Readings: The relation of hemoglobin to the red cell sedimentation findings was studied by Rubin and Smith (14) almost a decade ago. Most of their findings have been paralleled by our own experience. We found, for example, that a high hemoglobin count accompanied augmented sedimentation. Any diagnostician will agree that a high hemoglobin count, considered by itself merely serves to increase confusion, but if we can interpret it in terms of rapid cell sinking, it becomes at once a valuable diagnostic factor. The statement that "the hemoglobin content of the red blood cells parallels to a certain degree, the erythrocyte sedimentation reaction," was substantiated by our own experience. We have not kept a complete account of the relationship of the red cell count to the sedimentation results, but the few records regularly reveal a very close alliance—a low hemoglobin index implied augmentation in red cell sinking.

Achylia Gastrica: Though the differentiation between benign and malignant achylia is quite well standardized, the red cell sedimentation test should be of service in the diagnosis of this condition. The sedimentation rate has been shown to be unaltered in benign achylia, but increased in the malignant forms. True achlorhydria may be benign in a benign gastric tumor, when the sedimentation rate will be normal. But should the nature of the growth change, as in that mentioned by Sanders (15), demonstrated by Rubin at Montifiore Hospital, when the tumor develops central necrosis, or becomes infected, a rapid sinking of the red blood cells will be immediately perceptible. And the rapidity of this sinking will furnish an index of the extent and severity of malignant tissue destruction. The achylia of syphilis or pernicious anemia, or that frequently associated with a tuberculous infection, if estimated by the red cell sedimentation test, must be interpreted in terms of these respective maladies.

Bleeding and Non-Bleeding Peptic Ulcer: The anemia resulting from a bleeding gastro-duodenal ulcer alters the normal sedimentation rate. When bleeding ceases, the rate of red cell settling approaches normal, and thus points to a propitious time for surgery, if the case be one where surgery is otherwise indicated. This analogy holds good for mucus colitis, as well as cholelithiasis, both uncomplicated, or with attending inflammation.

The cases included in the first part of our Table presented generally similar characteristics: Hyperchlorhydria, a hemoglobin index ranging from 36 to 54 per cent, a red cell count of from 2.5 million to 3 million, and a sedimentation rate between 22 mm. and 38 mm. in 60 minutes. The duodenal cases showed the classic syndrome of a post-pyloric lesion, marked hyperchlorhydria with persistent deformity of the bulb, though the lesion did not cause obstruction and did not bleed; a hemoglobin index of 95 per cent, and a red cell count of five million. The sedimentation rate was regularly a horizontal line—2.2 mm. in 60 minutes. The value of the red cell sedimentation test in such instances is certainly obvious.

In the tedious period of convalescence which marks these ulcer cases, the test serves as a continual guide and check upon treatment. Should erosion of a blood vessel bring about sudden hemorrhage, the extent and activity of the bleeding, with the degree of tissue destruction involved will be registered in the behavior of the erythrocytes every time the test is applied. After surgical intervention, an increased sedimentation rate indicates the amount of traumatic tissue damage and the different phases of the absorption process. A persistently high sedimentation rate gives strong evidence of the existence of a complication. Yet the test must not be regarded as a substitute for blood cytology. Indeed, it is not a *substitute* for anything. It is an *addition* to all the previously employed methods. It even has psychic aspects. Gallagher (16) has employed it to detect evidences of chronic disease in subjects whose past history suggests the possibility of its existence. He avers that "The finding of a normal sedimentation rate has given us greater confidence in the advisability of expectant treatment, and in our attempts to reassure the patient."

Anemia Due to Colon Malignancy: Differentiating the various degrees of anemia due to bleeding of malignant lesions in the colon, necessitates taking into consideration the precise location of such lesions. As Heald (17) has put it, "The blood picture differs with the location of the lesion. It is a well established fact that secondary anemia is more marked with right side tumors than with left." The right half of the colon is of greater calibre, permitting larger growths to develop with more bleeding surface, and a resultant higher grade anemia. In the right half moreover, adenocarcinoma is the prevailing type of neoplasm, in contrast to the annular, constricting type likely to be found in the left half of the colon. Since the rate of red cell sedimentation varies with the degree of anemia, a higher rate would, therefore, point to a malignant lesion in the *right* colon. A large bleeding surface in the right colon may induce a blood picture readily mistaken for that of pernicious anemia. In this type of case every "lead" is of value, and the application of the sedimentation test may give invaluable evidence as to the location and extent of the lesion, and the severity of the tissue destruction—perhaps even resulting in a saving of priceless time sufficient to evert a fatal termination of the disease.

To the gastro-enterologist, as to medical practitioners in all divisions of the science, the red cell sedimentation test should prove an invaluable aid. While alone and unsubstantiated, it will not serve for differential diagnosis, or even demonstrate the presence of any given disease, nevertheless it serves to warn the clinician that disease of some kind is present. As the speed with which the red corpuscles sink is in direct proportion to the intensity of this disease process—though we must allow for the factor of anemia—a *postive* finding is a most valuable aid in diagnosis, even if a negative result does not necessarily indicate that *no* disease is present.

CONCLUSIONS

1. The red cell sedimentation test merits a place in the diagnostic equipment of the gastro-enterologist, as an aid in the diagnosis of diseases in which infection or tissue destruction are important factors.

2. Where no direct external evidence of disease exists, but the test shows a departure from normal conditions, the examiner will be stimulated to further scrutiny of the available evidence. This is of particular importance where a neurasthenic state, or frank neurosis is present, as under these conditions a normal sedimentation rate will assure the examiner

that he is not overlooking a physical ailment which is masked by the psychic state.

3. The test does not supplant any diagnostic measure now employed, but provides additional confirmation of their findings.

4. Though the present study is admittedly limited in respect to the number of cases, it offers convincing evidence as to the value of the test in determining the activity or latency of a malady, giving information as to tissue breakdown such as occurs in malignancy, or if inefficiency of the blood-forming mechanism, as in anemia due to excessive hemorrhage.

5. Since many wholly unrelated pathologic conditions produce symptoms apparently referable to the gastro-intestinal tract, the routine application of this test should operate to separate those cases within the gastro-enterologist's province from those which properly belong to other specialists. To illustrate: If the gastro-intestinal examination showed no lesion in the canal, a normal stomach chemistry, and an X-ray film without filling defects or other evidence of pathologic distortion, then an accelerated sedimentation rate should at once stimulate a search for a disease condition unrelated to the digestive canal.

6. The red cell sedimentation test resembles the leucocyte count in that it is not specific for any disease even when positive, and if negative does not necessarily indicate that *no* disease condition is present.

7. In the presence of a known pathological condition normal sedimentation indicates that the disease process is inactive; a speedy sinking of the red corpuscles indicates that the converse is true. The test can, therefore, be utilized as an aid in prognosis.

8. The present study is based on 100 consecutive clinic cases wherein the sedimentation test was employed, and upon the results obtained by applying the test to 22 normal individuals who volunteered to act as controls.

The writers wish to express their appreciation of the help and interest of Dr. Addie Stanford in the work here recorded, as well as to the members of the graduating class of 1935, without whose assistance it could not have been brought to an adequate conclusion.

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Bacteriological Findings in Disease of the Biliary Tract*

The Relationship of Gastric Acidity to Biliary Tract Infection

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THE determination of infection of the biliary tract has presented such a variety of technical difficulties that there are no published reports in which the diagnostic value of biliary tract drainage has been entirely confirmed. A further complication of this situation is that there is little information available as to biliary tract infection and its relationship to gastric acidity. Whipple (1) in a series of 25 patients going to operation reported that organisms similar to those found in cultures of the biliary tract were obtained in the pre-operative duodenal drainage bile in 54%. This percentage of accuracy in diagnoses suggests that the duodenal drainage findings represent a casual rather than a diagnostic relationship to the actual conditions of infection in the biliary tract. Lyon (2) in another series reported a majority of cases showed similar findings, no definite figure being available. Among others Boardman (3) and Nauss, Lake and Torrey (4) have questioned the value of

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sterile cultures of duodenal bile on the basis of comparison with clinical findings and known results of cultures obtained at operation.

Hanssen and Yurevich (5) have shown the great discrepancy between the numerous varieties of bacteria reported in cultures of duodenal bile and the few actually found in the biliary tract at operation. These authors found that, in a study of 104 patients coming to operation, the biliary tract was sterile in 67 per cent. Where infection occurred a single variety of organism was found in 95% of the cases. Biliary tract drainage of these patients, on the other hand, showed sterile cultures in only 25% of the drainages and a high proportion of mixed cultures. Agreement between drainage and operative findings occurred in 54% of the cases. While it is obvious that although the drainage findings showed the same apparent confirmation as in other series, here the bacteriological findings were actually of little diagnostic value.

In view of the unsatisfactory status of duodenal drainage as a means of determining biliary tract infection, an improved method of taking sterile cultures of duodenal bile, using an encapsulated tube, was recently devised and described by Twiss and Phillips (6). The purpose of this method is to eliminate contaminations of the bile externally, and internally by sealing off the duodenal tube while it passes through the mouth and stomach. In a series of patients studied by both this method and by a modification of the one of Lyon (7), (elsewhere described) (8), the encapsulated method showed in the duodenal bile only a third as many varieties of organisms similar to those of the mouth, three times the number of sterile cultures and half the number of mixed cultures. The fact that even findings with this method have not been entirely in accord with operative findings has led to further investigation.

The pathway of the pathogenic bacteria into the alimentary canal has been well described. Data on the bacteriology of the mouth, showing the prevalence of organisms in the crypts and salivary secretions, has been summarized by Arnold and Stuart (9). These authors have noted the impossibility of sterilization of the mouth, as has Boardman (3). The many bacteria gaining access to the stomach with saliva and ingested food have been described by Cotton (10) and Kopeloff (11). The usual presence of bacteria in the stomach with achylia was shown by Rehfuss (12).

TABLE I

Varieties of bacteria found in duodenal drainages of 355 patients. Patients are classified according to findings of free hydrochloric acid in the fasting gastric contents

Group	Achlorhydria Patients		Normal Acidity Patients		Hyperacidity Patients		Total	%
	No.	%	No.	%	No.	%		
No. of patients	87	100	172	100	96	100	355	
No. of drainages	193		220		107		550	
No. patients sterile	25	28	41	24	46	47	112	31
No. patients infected	62	72	131	76	50	53	234	69
Mixed cultures	56	64	41	24	10	10	120	33
Streptococcus non-hemolyticus	17	19	9	5	8	8	34	9
Staphylococcus albus and aureus	18	19	8	5	5	5	31	8
Contaminants (mouth); micrococcus, diphtheroids, etc	8	9	6	3	3	3	17	4
Yeasts	5	5	18	10	4	4	27	7
B. coli group	5	5	9	5	1	1	15	4
B. proteus	1	1			1	1	2	0.5
B. pyocyaneus	1	1			1	1	2	0.5
Strep. hemolyticus	0		2				2	0.5
Total	55	63	52	30	23	24	130	

Group I Achlorhydria — Free hydrochloric acid 0
Group II Normal Acidity — Free hydrochloric acid 0 to 20
Group III Hyperacidity — Free hydrochloric acid over 20

The normal variations in the amount of free hydrochloric acid in the gastric contents have been described by Vanzant, Berkson and Alvarez (13), whose "normograms," based upon the study of 3,746 normal subjects, show that in the age group from 20 to 75, the mean hydrochloric acid of the stomach is in males, 33-47, in females, 31-33. A further study has been made of gastric acidity associated with disease of the gall bladder by Vanzant, Alvarez, Berkson and Eusterman (14). These authors studied 602 patients operated upon, with and without stones, and concluded that although there was a slight increase in the incidence of patients with achlorhydria, in general there was little deviation from the normal in either men or women.

The normal duodenum in the fasting state has been shown to be sterile by Cushing and Livingood (15), Mac Neal and Chace (16), Kellogg (17) and others. The protective bactericidal power of the gastric secretion in maintaining the sterility of the upper intes-

tinal tract, ascribed mainly to the presence of free hydrochloric acid, has been noted by Hurst (18), and suggested by the duodenal drainage findings of Bartle and Harkins (19), who found in a study of 200 patients that the duodenal bile was sterile in 35% of the hyperacidity patients and 20% of those having an achlorhydria. A summary of the findings of a higher incidence of bacteria in the duodenal bile in patients having an achlorhydria has been given by Nauss, Lake and Torrey (4). Hurst (18) reported in a series of patients with gall stones that 49% had achlorhydria and 23% hyperchlorhydria.

The only investigation which the authors have found in which the bacteriological findings at operation have been correlated with the gastric acidity of each patient is that of Moynihan (20), who found in a series of 81 patients hyperchlorhydria in 20% and achlorhydria in 22%. In the achlorhydria cases the gall bladder bile showed infection in 66%, in those patients having a normal or increased hydrochloric acid the incidence of infection was 28%. Moynihan interprets these results as indicating that infection through the duodenum does occur and that this is more likely to occur with achlorhydria. This author agrees with Knott (21) that the probable mechanism is that the lack of free hydrochloric acid results in a loss of the "germicidal barrier."

A relationship between bacteriological cultures of bile obtained by means of the duodenal tube and the acidity of the gastric contents was also suggested by our own studies, in which wide variations in the bacteriological findings of the duodenal drainage bile were noticed in studying different groups of patients. These differences were found to coincide with the variations in gastric acidity, those patients having gastric hyperacidity were found seldom to show viable bacteria, while the majority of the positive cultures of duodenal bile seemed to occur in those having a diminished or absent free hydrochloric acid.

TABLE II

A study of duodenal drainage findings, comparing the results of cultures obtained by the un-encapsulated and encapsulated drainages in the same patients in regard to the relative incidence of sterility and mixed growths of bacteria

Group	Achlorhydria Patients		Normal Acidity Patients		Hyperacidity Patients			
	No.	%	No.	%	No.	%	Total	%
Unencapsulated Method								
Sterile	20	11	60	34	60	61	140	30
Mixed growth	82	44	45	25	5	5	132	28
Encapsulated Method								
Sterile	6	26	16	39	14	66.6	36	42
Mixed growth	8	35	1	2	0	0	9	10

AUTHORS' STUDY

During the past five years 2000 patients suspected of having disease of the gall bladder have been studied in the combined Medical and Surgical Clinic for Diseases of the Liver and Biliary Tract of the New York Post-Graduate Hospital. The purpose of the present article is to present the bacteriological findings of the duodenal bile in a series of 355 patients, classified according to gastric acidity, upon whom cultures of the duodenal bile were made in 550 drainages under sterile precautions. A further series of 120 patients was

TABLE III

Incidence of infection shown at operation. The number of patients showing positive cultures of the biliary tract, classified according to acidity of the gastric contents

Group	Achlorhydria Patients		Normal Acidity Patients		Hyperacidity Patients			
	No.	%	No.	%	No.	%	Total	%
Total No. of patients	50	100	47	100	23	100	120	
No. patients infected	23	46	10	21	7	31	40	33
Non-Calculous cases, Total No.	19	38	19	40	10	43	48	40
Infected	8	42	3	15	4	40	15	31
Calculous cases, Total No.	31	62	28	60	13	57	72	60
Infected	15	48	7	25	3	23	25	35

studied, in whom cultures of the gall bladder bile, the gall bladder wall, the cystic duct node, and stones if present were made at the time of operation. The results of cultures from operative specimens and from the duodenal bile in relation to the gastric acidity are given for 86. Bacteriological cultures of the duodenal bile and operative specimens were made under the direction of Dr. Adele Sheplar, according to the methods described by Hanssen and Yurevich (5).

In this study, we have arranged our patients into three groups on the basis of the amount of free hydrochloric acid found in the fasting gastric contents at the time biliary drainage was performed. In practically all cases, the drainages were done repeatedly. We have placed in Group I all patients showing no free hydrochloric acid in the fasting gastric contents, indicating a deficiency in free hydrochloric acid. Group II includes those having an average amount of free hydrochloric acid, with readings from 0 to 20. (The number of c.c. of N 10 NaOH required to neutralize 100 c.c. of gastric contents). This group corresponds to the normal acidity group of Alvarez and his associates. The fasting gastric contents are considered to have approximately half the amount of free hydrochloric acid shown in the fractional test meal. All patients having free hydrochloric acid over 20, which we consider a relative hyperacidity, are placed in Group III.

The bacteriological findings in the duodenal bile cultures of 355 patients not coming to operation are shown in Table I. The hyperacidity group here shows an incidence of sterile cultures nearly double that of the achlorhydria and normal acidity groups. The incidence of mixed cultures in the achlorhydria group is 6 times that of the hyperacidity group. In those patients showing only one or two varieties of bacteria, the achlorhydria group showed an incidence of infection more than double that of either of the acidity groups. The staphylococci and streptococci predominate in all groups, particularly with achlorhydria, where mouth contaminants are also more prevalent

TABLE IV

Frequency of occurrence of organisms in the biliary tract at operation, in patients classified according to gastric acidity

Group	Achlorhydria Patients		Normal Acidity Patients		Hyperacidity Patients		Total
	No.	%	No.	%	No.	%	
B. coli group	13	26	4	8	2	8	19
B. typhosus	3	6	2	4	2	8	7
Strep. non-hemol.	7	14	1	2	1	4	9
Staphylococcus aureus and albus	4	8	1	2			5
B. Welchii	0		2	4	0		2
B. proteus	0		0		2	28	2
Total	27		10		7		44
Total No. patients	50		47		23		120
Incidence of infection		54%		21%		30%	

TABLE V

Varieties of significant organisms found in the pre-operative specimens of duodenal bile, patients classified according to gastric acidity

Group	Achlorhydria Patients		Normal Acidity Patients		Hyperacidity Patients		Total
	No.	%	No.	%	No.	%	
B. coli group	6	12	7	14	0		13
Streptococcus non-hemolytic	2	4	3	6	1	4	6
B. typhosus	2	4	1	2	2	9	5
Staphylococcus							
Albus	0		5	10	0		5
Aureus	0		1	2	0		1
B. proteus	0		0		1	2	1
B. fecalis alkigenes					1	2	1
Total	10		21		6		
Total number of patients	50		47		23		
Incidence of infection		20		44		26	

B. coli, however, shows a definitely increased incidence in the achlorhydria and normal acidity groups.

A comparison of these findings with the operative bacteriological findings in a series of our patients, as shown by Hanssen and Yurevich (5), indicates again a wide discrepancy between the incidence of infection in the duodenal bile cultures and those cultures taken at the time of operation.

The results of duodenal cultures taken by means of the encapsulated tube are therefore shown with those of the unencapsulated method in Table II. Here we see that the encapsulated method shows cultures more in accord with the operative findings, the percentage of sterile cultures being higher in all groups and reaching 66% in the hyperacidity group. As before stated, 67% of the patients showed sterile cultures of all parts of the biliary tract at operation. It is further worthy of note that although the bacteria in general were the same as found by the other method, practically no mixed growths of bacteria, indicating contamination, were obtained by the encapsulated method in patients having free hydrochloric acid in the gastric contents. Of 5 patients in whom the biliary tract was sterile at operation, having pre-operative duodenal drainage by the encapsulated method, 4 showed sterile cultures in all specimens.

To determine the actual incidence of biliary tract infection and its relationship to gastric acidity a study was made of 120 patients operated upon, the findings are shown in Table III. The series as a whole showed a distribution of 40% of the cases in both Groups I and II, 20% in Group III. Of the entire group 60% of the patients showed calculi. The incidence of infection in the calculous and non-calculous groups was approximately the same as in the whole group, indicating no definite relationship between infection and the presence of gall stones. On the other hand a definite relationship is suggested between gastric acidity and the presence of infection, as well as stones. In the achlorhydria group the incidence of infection is approximately twice that of the normal acidity group, the achlorhydria group also showing a somewhat higher proportion of calculous cases.

The varieties of bacteria found in the biliary tract at operation are shown in Table IV. In the achlorhydria group the incidence of infection is seen to be nearly twice that of the hyperacidity group and nearly three times that of the normal acidity group. Bacteria were found more frequently in the gall bladder bile of those patients having stones who were deficient in free hydrochloric acid than in those having no stones. The bacteria found may be grouped into those occurring predominantly in the achlorhydria group, which include the colon infections, the streptococci, and staphylococci. The only organisms occurring both with and without gastric acid are those of the typhoid and colon groups and the streptococcus non-hemolyticus. The third group, found only in those patients having free hydrochloric acid in the gastric contents, include the B. Welchii and the B. proteus.

It is here interesting to note that the organisms found in those patients having free hydrochloric acid are those which would apparently be little affected by gastric acid. The B. Welchii and B. proteus are known to be found normally in the liver, while the colon infections are considered to be brought to the liver through the portal system. Typhoid infections are usually considered to be of hematogenous origin. Knott (21) has also shown that typhoid and colon organisms are more resistant to the bactericidal action of acid in bile. The streptococci and staphylococci, however, seem in most cases to have been prevented from gaining access to the alimentary tract by the free hydrochloric acid in the stomach.

The results of duodenal drainage in the operative patients are shown in Table V. The bacteria here listed were found in the duodenal bile either in pure cultures or with not more than one other variety of organism. A comparison of the duodenal drainage cultures with the operative findings shows that in the achlorhydria group not all the varieties of staphylococci, streptococci and colon organisms occurred in pure growth in the duodenal bile, but were present as mixed growths of bacteria. In the normal acidity group the duodenal drainage findings were in most cases in accord with the operative, except that the staphylococcus albus was found in the duodenal drainage bile 5 times when not present in the biliary tract at operation. In the hyperacidity group the B. coli was not grown in the duodenal bile due probably to the inhibitory action of the free hydrochloric acid.

TABLE VI

A diagnostic comparison of pre-operative duodenal drainage cultures with the operative findings in 16 patients showing infection of the biliary tract at operation

Group	Achlorhydria	Normal Acidity	Hyperacidity	Total
No. of patients	10	3	3	16
Cultures identical with operation				
B. typhosus	2	1	2	
B. coli	3	0	0	
Streptococci	1	0	0	
Sterile	0	0	0	

Of the 41 patients found to have a sterile biliary tract at operation, duodenal drainage cultures were sterile in 14% of the patients in Group I, 38% of those in Group II, 72% of those in Group III. It is here apparent that the duodenal cultures were contaminated 5 times as frequently in the achlorhydria group as in the hyperacidity group. All patients having sterile cultures of duodenal bile were sterile at operation. In the 16 patients showing infection at operation, (Table VI) significant duodenal cultures were found in 9 or 56%. The majority of those patients showing a mixed growth or different type of organism, were in the achlorhydria group. The only organism present in the biliary tract at operation, found in pure culture in the duodenal bile, were those of the B. coli groups, the B. typhosus, and the streptococci. None of the patients showing infection of the biliary tract were drained by the encapsulated method.

SUMMARY

1. A survey is presented of the bacteriological findings of 355 patients upon whom sterile drainages were done and 120 patients operated upon for disease of the biliary tract, where cultures were made at the time

of operation of the gall bladder bile, the gall bladder wall, the cystic duct node, and stones if present. These patients are classified in relation to the gastric acidity of each.

2. In the 355 patients not coming to operation the incidence of sterile cultures of the duodenal bile in those having a hyperacidity was double that of the patients with an achlorhydria or a normal acidity, mixed cultures occurred 6 times as frequently in those with achlorhydria.

3. In the duodenal drainages performed upon the same patients by the encapsulated method, a higher percentage of sterile cultures were obtained in all groups. Practically no mixed cultures were obtained by this method in those patients having free hydrochloric acid in the gastric contents.

4. In 120 patients having had cultures of the biliary tract at operation, the incidence of infection in those with an achlorhydria was found to be about twice that of the group with a normal acidity. In this series the incidence of infection was the same in the calculous and non-calculous groups.

5. According to the number of varieties of bacteria found in the biliary tract at operation, the group of patients with an achlorhydria showed twice the number found in the group having hyperacidity and three times the number in the group having a normal acidity.

6. A study of the diagnostic value of duodenal drainage showed that in this series (1) in every case where the duodenal drainage cultures were sterile, the biliary tract was sterile at operation. (2) In no case where infection was present in the biliary tract were the duodenal bile cultures sterile. (3) In patients in whom the biliary tract was sterile at operation but who showed organisms in the duodenal drainage bile, most of the contaminations occurred in the achlorhydria group. (4) In patients with an infection of the biliary tract, the only organisms found preoperatively in pure cultures were those of the B. coli, B. typhosus, and streptococcus groups. (5) The staphylococcus albus, although found quite frequently in the duodenal drainage bile, was not found in the biliary tract of the same patients.

CONCLUSIONS

1. There is a definite relationship between gastric acidity and biliary infection, proved by pre-operative determination of gastric acidity and bacteriological studies of the biliary tract at operation.

2. Cultures of duodenal bile obtained by the encapsulated method show results more in accordance with operative findings in the same patients.

3. Interpretation of the results of sterile cultures of duodenal bile should be made only with a knowledge of the gastric acidity in each case.

The authors wish to express their indebtedness to Doctors Charles Gordon Heyd, Edward F. Peterson and R. Franklin Carter, for their permission to use the data concerning operative patients and cultured specimens, to Dr. Adele Sheplar for her collaboration in regard to the bacteriological work, and to Dr. Carl H. Greene for assistance in the presentation of this material.

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SECTION II—*Experimental Physiology*

The Fate of Bacteria Injected Directly into the Cecal End of the Colon*

By

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MANY investigators have studied the fate of various bacteria, pathogenic and non-pathogenic, in the gastro-intestinal tract of man and animals. The usual method of carrying out this type of experiment has been to feed the organisms under investigation by mouth and then to attempt to isolate them from the feces of the experimental animals. This procedure involves great difficulty in the interpretation of results obtained: if the organisms do not appear in the stool, it is impossible to determine in what part of the gastro-intestinal tract they were destroyed. From the standpoint of the clinical investigator, this type of experiment is important, since in the usual types of enteric infections the causative organisms are ingested. However, to the experimenter interested in the physiology and bacteriology of the gastro-intestinal tract, it is of great importance to know in what portion of the intestine the lethal action, if there is such, is resident.

Various investigators have devised operations upon animals which allow the experimenter to introduce and remove substances from different levels of the intestinal tract. One of the most common operations of this type is the one by which a fistula is made in the cecum. Various objections to this type of operation have been made on the grounds of leakage and improper functioning. An improved method of making a cecal fistula has been devised by Cowgill and Weinstein (to be published) which eliminates the objections commonly made against the cecal fistula. Having on hand what we believed to be the ideal animal, the writer undertook to perform the experiments here reported. It was his purpose in this work to study the effect of the colon on bacteria introduced directly into it.

EXPERIMENTAL

Three dogs having the type of cecal fistula devised by Cowgill and Weinstein were used as the experimental animals. There was a minimum of leakage from the intestinal operative site; furthermore, the dogs were in an excellent state of nutrition throughout the course of the experiments.

The experiments were carried out under two different conditions. First, organisms were introduced into the colon when the dogs were on a diet consisting of lactose, bread and grains, and consequently harbored a large percentage of *L. acidophilus* in their intestines; and second, when the animals were on a strict meat diet and eliminated no demonstrable lactobacilli in their feces.

The organisms studied were *Ser. marcescens*, *S. lutea*, and *B. mycoides* (vegetative and spore forms). All of these were chosen because they could be identified easily in plate culture either by their color production or colony morphology. The organisms were grown on meat extract agar plates at their proper growth temperatures. The growth from two Petri plates was suspended in 5 c.c. physiological saline solution and instilled through the cecal fistula directly into the colon by means of a catheter and a 10 c.c. syringe. The animals were under continuous observation for a half hour after injection, to make certain that none of the instilled material leaked back through the fistula opening.

Both young (spore-free) and old (spored) cultures of *B. mycoides* were used. The absence or presence of spore forms was always checked by making a spore stain of the material to be introduced into the colon. When only spore forms were required, a suspension of a well matured culture of *B. mycoides* was heated at 80° C. for ten minutes before use. In culturing the feces for *B. mycoides*, cultures of both the heated and the unheated fecal emulsions were made.

At intervals of 24, 48, 72 and 96 hours after cecal injection, fecal material was obtained from each animal. One or more specimens of feces were emulsified in a small amount of physiological saline solution, and from one to two cubic centimeters of the suspension streaked on the proper media for identification of the organism sought. The cages in which the animals were kept were cleaned with soap and hot water immediately after each collection of feces, in order to eliminate possible contamination from this source.

EXPERIMENTS WITH DOGS HAVING A HIGH ACIDURIC INTESTINAL FLORA

The dogs were kept on a high carbohydrate diet for three weeks, at the end of which time they showed a high proportion of *L. acidophilus* in the feces; the bacterial injections were then made into the colon through the cecal fistula. Throughout this study, examinations were made every other day for the presence of the lactobacilli.

Ser. marcescens and *S. lutea* could at no time be recovered from feces of animals into which they had been injected by way of the cecum. Cultures of the fecal material made as early as 6 hours and as late as 96 hours after injection failed to reveal the presence of either of these organisms.

B. mycoides, however, gave entirely different results. When the vegetative cells were injected into the cecum

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they were recovered in one dog as late as 48 hours after injection and in the other two animals even 72 hours after instillation. In no instance was it possible to recover them from the feces 96 hours after they had been introduced into the colon. When the unheated vegetative cells were employed, fecal suspensions showed the presence of *B. mycoides;* whereas, heated feces (10 minutes at 80° C.) never revealed the organism in culture. In other words, when vegetative *B. mycoides* cells were introduced directly into the colon by way of the cecal fistula only vegetative cells could be recovered from the feces.

Heated suspension of spore-containing cultures of *B. mycoides* instilled into the colon of the animals led to the recovery of the organism after 72 hours in two dogs and after 48 hours in the third animal. Cultures taken 96 hours after injection always failed to show the presence of the organism in the fecal material. In contrast to the results obtained following the injection of the vegetative cells, *B. mycoides* could always be cultured from the *heated* feces of the dogs which had been injected with the spores of this organism.

EXPERIMENTS WITH DOGS HAVING NO LACTOBACILLI IN THE INTESTINE

The dogs were kept on a purely meat diet until fecal examinations revealed the complete absence of *L. acidophilus.* The injection experiments were begun after an additional week on this diet.

The same results were obtained in this experiment with *Ser. marcescens, S. lutea* and the two forms of *B. mycoides* as in the experiments conducted when the dogs harbored an intestinal flora high in *L. acidophilus;* the first two organisms failed to appear in the feces at any time, while vegetative cells of *B. mycoides* appeared as vegetative forms, and the spores as spores in the fecal material.

DISCUSSION

Ample evidence has been obtained in this investigation to show that the large intestine of the dogs is capable of killing bacteria introduced directly into it. The cause of this lethal action is, of course, a debatable question.

Some objection may be raised to this work on the ground that no organism of purely intestinal origin was used. This procedure was necessary, it seems, since it would be impossible to detect the presence of common intestinal organisms introduced through the fistula in the feces because of the occurrence of the bacteria normally in the intestine. The use of some of the pathogenic intestinal organisms was contemplated, but this plan was soon discarded, because of the possibility of serious injury to the valuable experimental animals. However, experiments of this type are being contemplated.

TABLE I

Showing fate of different bacteria when injected directly into the colons of dogs

Dog No.	Organisms Injected Into Colon															
	Serratia Marcescens				*S. lutea*				*B. mycoides*, vegetative cells				*B. mycoides* spores			
	24 hrs.	48 hrs.	72 hrs.	96 hrs.	24 hrs.	48 hrs.	72 hrs.	96 hrs.	24 hrs.	48 hrs.	72 hrs.	96 hrs.	24 hrs.	48 hrs.	72 hrs.	96 hrs.
1	0	0	0	0	0	0	0	0	+	+	+	—	+	+	—	—
2	0	0	0	0	0	0	0	0	+	+	+	—	+	+	+	—
3	0	0	0	0	0	0	0	0	+	+	—	—	+	+	—	—

Organisms Injected Into Colon

From the evidence obtained with *B. mycoides* it appears that, even though the organisms may pass through the large intestine alive, they do not multiply. Evidence for this statement is the fact that when vegetative cells of *B. mycoides* were injected into the colon only vegetative cells could be recovered from the feces, while the instillation of spores through the cecal opening always led to the recovery of spores in the feces of the dogs.

SUMMARY

Serratia marcescens and *Sarcina lutea* could not be recovered from the feces of animals into whose colon they were injected through a cecal fistula. This finding was the same whether the intestinal flora of the experimental animals was high or low in its *L. acidophilus* content.

B. mycoides could be recovered from the feces of dogs as late as 72 hours after injection; when vegetative cells were injected, only vegetative cells were recovered; whereas, when spores were introduced, spores were recovered. These findings were apparently independent of the status of the animals' natural intestinal flora.

The Nature of Peptic Ulcerations*
The Factor of Spasm

By

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NUMEROUS investigators have been successful in producing ulcers of the jejunum by utilizing the Exalto (4) method of diverting the alkaline duodenal contents some distance below the gastrojejunal anastomosis. Steinberg (11) stripped the jejunum, anastomosed to the stomach, of about three-fourths of its longitudinal and circular muscle layers for a distance of ten centimeters (*Fig. 1*). *Such a procedure leaves* a narrow strip of muscle along the mesenteric border for the preservation of the blood supply to the jejunum. The above experiments were combined with an Exalto short-circuiting operation (Fig. 1). In the control experiments where the muscle layers are left intact an ulcer takes place in from 90 to 100 per cent

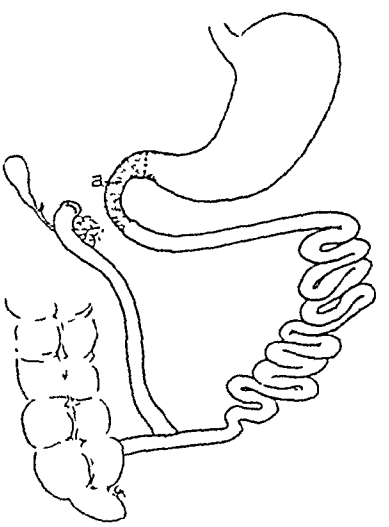


Fig. 1. The short-circuiting of the alkaline duodenal contents into the ileum. Muscle layer stripped for ten centimeters distal to the gastrojejunal anastomosis (a).

of the dogs operated by the Exalto method. Most of the ulcers are found one or two millimeters distal to the gastrojejunal anastomosis (Steinberg and Proffitt) (9).

Of sixteen dogs operated on with the Exalto short-circuiting operation, and with the muscle layers stripped, only three dogs developed typical ulcers of the jejunum one or two millimeters distal to the anastomosis. In five dogs ulcers were found ten centimeters distal to the gastrojejunal anastomosis, or exactly where the muscle layer began its normal course. This was the first time that ulcers were observed in this situation (Steinberg and Starr) (10) (Fig. 3).

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Subsequent to the publication of the first two papers ten dogs were again operated according to the Exalto procedure, and again with the muscle layers of the jejunum stripped. In only one dog was an ulcer found at the gastrojejunal anastomosis, and in three dogs small ulcerations were found ten centimeters distal to the gastrojejunal anastomosis and, again, exactly where the muscle layer began its normal course.

It was impossible to explain the findings on the theory of an impact since these ulcers took place ten

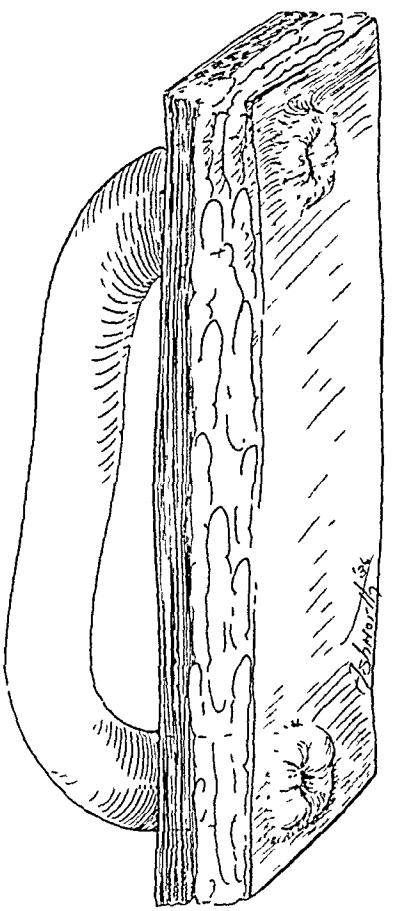


Fig. 2. A Thiry-Vella loop.

centimeters distal from where chyme is ejected by the pyloric sphincter. These ulcers which were never observed before were rather puzzling as to their nature. Inasmuch as no ulcers were observed where the muscle layers were stripped the spasm of the jejunum offered a plausible explanation. Apparently the stomach contents stagnate for a variable period of time in the part of the jejunum denuded of its muscle. When the contents reach the beginning of the jejunum with its in-

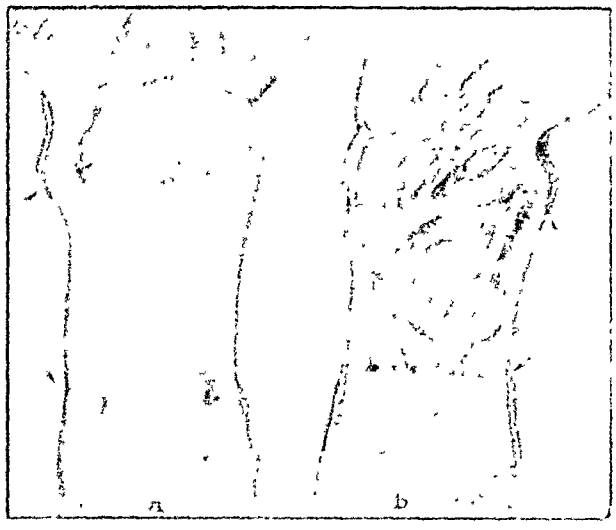


Fig. 3. A gastro-anastomosis (a) between the stomach and the jejunum with an Exalto short-circuiting operation. The area between the arrows shows where the muscle layer was stripped from the jejunum. A small ulcer near the pyloric valve and two chronic "kissing ulcers" exactly where the muscle layer begins its intact course, or about 10 cm. from the pyloric valve, are seen. On the peritoneal surface (b) of the same specimen the omentum covers the area in which the muscle is stripped.

tact layer of muscle a spasm takes place. Eventually the acid contents are neutralized and become acceptable to the distal jejunum.

In order to analyze the validity of the theory of spasm in relation to acid, we produced a Thiry-Vella loop (Fig. 2) about fifteen centimeters long and about fifteen centimeters distal to the duodenojejunal angle. After the recovery of the animals, a sponge, one centimeter long and about one-half of a centimeter wide, attached to a thread the length of the loop, was introduced into the proximal opening of the loop. (I. P. Quigley, W. H. Highstone and A. C. Ivy (7)). One hundred observations were carried out on five dogs. Some of the experiments were made with the sponge immersed in normal saline, while in others it was immersed in 0.15, 0.2, 0.3 and 0.4 per cent hydrochloric acid. One series of experiments with the sponge immersed in normal saline was immediately followed by another using the various strengths of hydrochloric acid. The results of these experiments, as carried out on five different loops, were remarkably consistent. As indicated by the Tables it is quite evident that the sponge immersed in hydrochloric acid produces a definite delay in its progress through the loop. The sponge immersed in 0.15, 0.2, 0.25 and 0.3 per cent hydrochloric acid brings about a more or less uniform delay in the progress of the sponge. On the other hand, three experiments with 0.4 per cent hydrochloric acid gave a rather bizarre result with either very prolonged delay or very rapid progress through the loop (Tables I and II).

It was observed that when the sponge immersed in saline was introduced into the proximal opening of the loop the dog offered no resistance and in most of the experiments was quiet. The secretion of the intestinal mucosa was not noticeable. On the other hand, in the experiments where the sponge was immersed in hydrochloric acid higher than 0.15 per cent, a copious secretion from the loop was produced. The protruding mucosa appeared pale and spastic. In a few experiments the dogs were restless, vomited and resisted the introduction of such a sponge. On certain occasions there was evidence that the sponge immersed in acid interrupted its normal course by a prolonged delay at some part of the loop.

It is impossible to minimize the importance of certain animal experiments (Steinberg and Proffitt) (9) since to a greater extent they represent a replica of the surgical procedures used in the treatment of gastroduodenal ulcerations. The primary ulcers of the jejunum are extremely rare. It is only after the gastro-enterostomy came into vogue that jejunal ulcers were beginning to be noticed with more frequency. A jejunal ulcer is being produced unwittingly with regularity in the patient by performing certain types of gastro-intestinal anastomoses. Some of the modern text books on surgery of the stomach and duodenum still recommend such operative procedures as the Roux anastomosis, the von Eiselsberg exclusion operation and also the Devine transection exclusion operation. One engaged in experimental surgery is able to produce typical postoperative jejunal ulcers in dogs by using the above mentioned procedures recommended to the surgeon as a cure for gastro-duodenal ulcerations, (Steinberg) (11). It is difficult to assume the presence of a constitutional predisposition in each one of these cases. It is more logical to attribute these jejunal ulcerations directly to the operative procedure. The various gastro-intestinal anastomoses in the dogs which produce typical jejunal ulcerations are therefore of great importance in elucidating some of the local factors responsible for the production of these lesions. These local factors do not exclude the importance of the constitutional predisposition, the disharmony of the vegetative nervous system or some form of an

TABLE I

Dog. No. 1B—2-12-35. Thiry Vella Loop
Progress of sponge from proximal to the distal opening indicated in minutes

Sponge immersed in normal saline before first trial only	Sponge immersed in .15% Hydrochloric before each trial
3-½	6
2	5-½
2-¼	6-½
3	6
3-½	5-½
3-¼	6
3	
2-½	
2	

endocrin imbalance. The experimental attack however, on the parasympathetic and sympathetic systems has not been conclusive. The only experiments which are under direct control are those which produce ulcers of the jejunum with a certain regularity by varying the anatomical and physiological relationships between the stomach and the jejunum. (Steinberg and Proffitt). The surgical procedures which give rise to postopera-

tive jejunal ulcerations are so closely related to the experimental procedures on the dog that by comparison there remains little doubt as to the true nature of the jejunal ulcerations in the human.

A vast amount of accumulated material on the experimental postoperative jejunal ulcerations is not

TABLE II

Dog No. 2—11-2-34. Thiry Vella Loop
Progress of sponge from proximal to distal opening indicated in minutes

Sponge immersed in normal saline before first trial only	Sponge immersed in .2% Hydrochloric before each trial
6	6
4	6
4	10
4	12
4	18
	28-½

without any importance as to the nature of duodenal ulcers, as will be seen from the analysis of our experiments. Shay and Gershon-Cohen (8) in a very exhaustive study on the control of the pylorus have demonstrated that the addition of certain strengths of hydrochloric acid, depending on the original state of the secretion, have a definite relationship on the emptying time of the stomach. These investigators have noticed antral spasm and pylorus spasm from duodenal instillation of hydrochloric acid. Dragstedt and Palmer (3) operating under local anesthesia have noticed a marked contraction of the circular muscle of the duodenum after the exposure of the duodenal ulcer to 0.5 per cent hydrochloric acid. The patient complained of a severe cramp-like pain in the stomach.

The frequency of "kissing ulcers" of the duodenum has been reported by many clinicians. O. Bsteh (1) has reported thirty-two "kissing ulcers" out of one hundred and ten duodenal ulcers. Hoffman (5) noticed these ulcers in forty to fifty per cent of his cases, and Clairmont (2) in seventy-five per cent. According to my own experience the frequency of multiple ulcers is more common than previously observed. Some of the ulcers are in the state of healing and some are so small that they are either not recognized or are destroyed during the removal of a part of the duodenum with the stomach. This fact may explain the discrepancy in the observations of various surgeons.

Most of the ulcers of the duodenum have a typical location distal to the pylorus and separated from it only by a few millimeters. They are frequently found opposite each other, and for this reason named by Moynihan "kissing ulcers" (Fig. 4). In the further progress these ulcers may extend to the lesser or greater curvature of the duodenum. They may also coalesce and lose their original form and position. The progressive changes make it difficult to recognize the original location in many specimens on account of deformity and the scarring of the duodenum. A thorough microscopic examination of the removed part of the duodenum would be interesting and perhaps more convincing as to the nature and location of these lesions.

The characteristic localization of these ulcers in the same segment and on the anterior and posterior walls, opposite each other, is significant. A few of these ulcers were observed by myself in the experiments where the muscle of the jejunum was stripped, had the appearance of the "kissing ulcers" of the duodenum in the human (Fig. 4) and were found in the same circular segment of the jejunum (Fig. 3). It has been pointed out in several previous communications that these ulcers were at the segment of the jejunum where the muscle layer began its normal intact course, and exactly ten centimeters distal to the propelling force of the pylorus (Steinberg; Steinberg and Starr) (10). A mechanical trauma as of etiological importance can therefore definitely be excluded.

The experimental and clinical evidence, particularly as it concerns the localization of duodenal ulcers and jejunal ulcers, is suggestive of a certain theory of a local mechanism. While the search for some dominant cause in the diencephalon, or in some endocrin imbalance, or both, is highly interesting, it does not explain the typical location of many of these ulcers. So far there is no conclusive evidence of a definite pathological condition existing in the brain of individuals suffering from peptic ulcerations. Periodicity of the symptom complex in itself would make some pretense of a denial that there is a continuous pathological process in the diencephalon. One is therefore hardly justified to go farther than the observation that hypersecretion, hypermotility and hypertonicity of the stomach are closely related to the ulcer symptom complex and that these conditions are frequently found in the young type of individuals. It may also be stated that the ulcer symptom complex is frequently initiated in an environment of strain, worry and other forms of mental upsets.

Ulcers do not occur in the duodenum or jejunum because the complicated nervous mechanism which controls the motility, secretion and blood supply are constantly found in a certain equilibrium. These three factors are closely related to each other and influenced by the nervous system. A disturbance of one com-

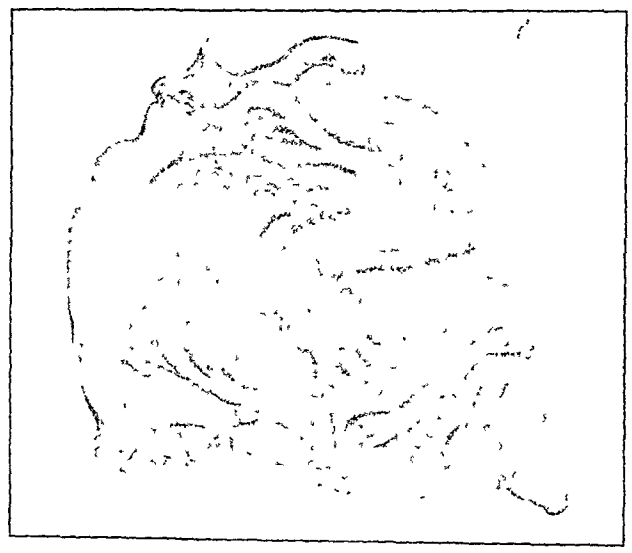


Fig. 4. Distal two-thirds of a stomach recently removed by the Author. "Kissing ulcers" in the duodenum which in their form and location closely resemble the experimental "kissing ulcers" in Fig. 3.

ponent influences the others. Clinically it is seen that there are definite cycles, crises and stimuli which are demonstrated in the functional disturbance of the stomach which finally lead to the formation of ulcer (Kalk) (6). Nor can one underestimate the importance of the equilibrium which also exists between the acid stomach and the alkaline duodenum or jejunum after a gastro-enterostomy. A gastro-intestinal anastomosis mobilizes the compensatory forces in order to maintain the necessary equilibrium between the stomach and jejunum. Under adverse conditions when the acidity of the stomach contents are abnormally high a jejunal ulcer or jejunitis takes place.

From the experimental work and clinical evidence there is sufficient support to consider hyperacidity, hypersecretion and spasm as a vicious circle. At times it is difficult to differentiate an acid gastritis or duodenitis from a duodenal ulcer. In fact a typical ulcer symptom complex may be present in the absence of a duodenal ulcer. A patient with a hyperirritable acid stomach under certain conditions is a candidate for a duodenal ulcer.

It is impossible to bring within the limits of a short paper the numerous theories advanced, or give credit to the important experimental work or to introduce much of the controversial material. Only factors under experimental control which closely parallel the clinical picture have been emphasized. It is because of these considerations that the gastric ulcer was left out, since thus far it does not seem to fit into this picture.

The experimental ulcers of the jejunum are produced with such ease by varying certain anatomical relationships between the stomach and the jejunum, based on the expected physiological changes, that a conception of the nature of these ulcerations becomes fully tangible (Steinberg and Proffitt).

A familiarity of these principles enables us to proceed "mutatis mutandis" with a rational medical and surgical treatment.

SUMMARY

In addition to a previous communication, ten more dogs were operated on according to the Exalto method and with the muscle of the jejunum stripped for an area of ten centimeters. Again, no ulcer took place where the muscles were stripped. In ten dogs operated on in this manner one ulcer was found one or two millimeters distal to the gastrojejunal anastomosis. In three dogs ulcers were found ten centimeters distal to the gastrojejunal anastomosis or exactly where the muscle area began its normal course. This interesting observation, reported elsewhere for the first time by the Author in another series of experiments, appears highly intriguing.

The progress of a sponge through a Thiry-Vella loop is definitely delayed when the sponge is immersed in hydrochloric acid ranging from 0.15 per cent to 0.3 per cent. The experiments with the Thiry-Vella loop are supportive of our previous contention that there is a close relationship between acidity and spasm of the jejunum and the etiology of the experimental ulcerations.

Emphasis is made upon the experiments of gastro-intestinal anastomosis which are in a greater part a replica of surgical procedures used in the treatment of peptic ulcerations. The typical jejunal ulcerations closely resemble the duodenal and postoperative ulcerations in the human.

No denial is made of the importance of the vegetative nervous system (diencephalon), and the endocrin glands or the constitutional type.

Emphasis has been made upon the equilibrium which normally exists between the stomach and duodenum and which may be disturbed in the individual with a certain constitutional predisposition and in an unfavorable environment. This initiates a local vicious circle of acid and spasm between the stomach and the duodenum or the jejunum in a gastro-enterostomy.

It is far from my intention to give these experiments and reflections a pretense of completeness and finality. It serves only to emphasize an interesting experimental observation and an attempt to explain the part which the local mechanism of the ulcer symptom complex plays as related to a general conception, as yet less tangible and so far experimentally, without conclusive evidence.

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Studies in Absorption of Undigested Proteins in Human Beings

VI. The Absorption of Unaltered Protein from the Abnormal Gastro-Intestinal Tract

By

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and

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IN earlier studies by Brunner, Sussman, Davidson and Walzer (1, 2), it was noted that, for unknown reasons, the rapidity of absorption of unaltered protein varied considerably in supposedly normal subjects. The findings in some patients with gastro-intestinal disease seemed to suggest a possible explanation for this phenomenon. It was noted that the absorption time in conditions which are usually accompanied by gastric hyperacidity seemed slower than in those in which hypoacidity usually exists. For this reason, an intensive study of the absorption phenomenon in abnormal cases seem warranted in order to obtain more definite information on the subject.

In the present investigation, a series of forty cases with functional or organic diseases of the gastro-intestinal tract were studied primarily for the purpose of determining whether a definite relationship exists between gastric acidity and the rate of absorption of unaltered protein following its oral administration. The majority of patients in this group had some form of disease of the upper digestive tract. The clinical diagnoses in these cases were arrived at as a result of operative procedures, X-ray examinations and laboratory studies. The gastric acidity was determined by a fractional gastric meal in approximately half the series and by a Boas-Ewald test meal in the remainder. In many instances, gastric analyses were repeated on several occasions in order to check abnormal findings, for, it is known that there may be variations in gastric acidity in the same individual depending upon such factors as the emptying time of the stomach, psychic disturbances, the amount of saliva swallowed, the type of test meal employed, regurgitation of duodenal contents, etc., (3, 4, 5, 6, 7, 8). The readings charted in Table I represent the acid values of gastric digestion determined in each case at the end of one hour following the ingestion of the test meal.

The technic for studying the absorption of unaltered protein is an immunologic one and is the same as that employed in previous studies with egg and fish antigens (9). Peanut was the protein chosen for investigation in the present series because a serum particularly suitable for the study of this antigen was available at the time.

Peanut was excluded from the diet of the subject for twenty-four hours preceding the experiment. The subject was then passively and locally sensitized on the forearm by the intracutaneous injections of .05 c.c. of a 1-10 dilution of "C" serum. This serum had been obtained from a patient who was extremely sensitive to peanut and who manifested a marked reaction to intracutaneous tests with this antigen in very high dilution. One or two days later, the subject reported early in the morning without breakfast for the peanut test meal. The latter consisted of a "milk" made by disolving 10 gms. of raw ground peanuts in 30 c.c. of water to which was added 1 gm. of sugar and .05 c.c. of oil of cloves. Shortly after the ingestion of this meal, a reaction developed at the sensitized site, which usually consisted of pruritis, erythema, and wheal formation. The onset of this reaction marked the entrance of the undigested peanut protein into the circulation.

The absorption time of each subject was measured from the time the test meal was taken to the first objective symptom noted at the sensitized site, namely, erythema or wheal. (See Table I). Although pruritis usually heralded the start of the local reaction, it was considered an unreliable starting point because it is a subjective symptom which cannot be detected by the investigator. A detailed description of the technic and local reaction have been presented in previous communications (9, 10).

Because atopic patients do not accept passive local sensitization normally and regularly (11), all patients with past, present or family histories of hay fever, asthma, or similar forms of atopy were excluded from this study.

For the purpose of analyzing the results obtained, the cases in this series were subdivided into four groups according to their acid values. Individuals who had a variation in free HCl between 20 and 30 degrees and a total acidity between 30 and 40 degrees were considered normal. A state of hyperacidity was considered present when the free HCl was constant at 40 degrees or over and the total acidity was constant over 60 degrees. Those in whom free HCl was constant at less than 10 degrees and the total acid was constant under 20 degrees were placed in the hypoacidity group. Individuals in whom no free HCl was present at any time comprised the anacidity group. The findings of Sagal, Marks and Kantor (12) in a study of 6679 test meals and those of Vanzant (13) and her co-workers who analyzed 3746 records of the Mayo Clinic, justify this broad classification of cases into four groups, according to the degree of gastric acidity.

The results of the studies on protein absorption obtained on the nine patients in this series who have normal gastric acidity values have been grouped in Table II. The shortest absorption time among them

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tive jejunal ulcerations are so closely related to the experimental procedures on the dog that by comparison there remains little doubt as to the true nature of the jejunal ulcerations in the human.

A vast amount of accumulated material on the experimental postoperative jejunal ulcerations is not

TABLE II

Dog No. 2—11-2-34. Thiry Vella Loop
Progress of sponge from proximal to distal opening indicated in minutes

Sponge immersed in normal saline before first trial only	Sponge immersed in .2% Hydrochloric before each trial
6	6
4	6
4	10
4	12
4	18
	28-½

without any importance as to the nature of duodenal ulcers, as will be seen from the analysis of our experiments. Shay and Gershon-Cohen (8) in a very exhaustive study on the control of the pylorus have demonstrated that the addition of certain strengths of hydrochloric acid, depending on the original state of the secretion, have a definite relationship on the emptying time of the stomach. These investigators have noticed antral spasm and pylorus spasm from duodenal instillation of hydrochloric acid. Dragstedt and Palmer (3) operating under local anesthesia have noticed a marked contraction of the circular muscle of the duodenum after the exposure of the duodenal ulcer to 0.5 per cent hydrochloric acid. The patient complained of a severe cramp-like pain in the stomach.

The frequency of "kissing ulcers" of the duodenum has been reported by many clinicians. O. Bsteh (1) has reported thirty-two "kissing ulcers" out of one hundred and ten duodenal ulcers. Hoffman (5) noticed these ulcers in forty to fifty per cent of his cases, and Clairmont (2) in seventy-five per cent. According to my own experience the frequency of multiple ulcers is more common than previously observed. Some of the ulcers are in the state of healing and some are so small that they are either not recognized or are destroyed during the removal of a part of the duodenum with the stomach. This fact may explain the discrepancy in the observations of various surgeons.

Most of the ulcers of the duodenum have a typical location distal to the pylorus and separated from it only by a few millimeters. They are frequently found opposite each other, and for this reason named by Moynihan "kissing ulcers" (Fig. 4). In the further progress these ulcers may extend to the lesser or greater curvature of the duodenum. They may also coalesce and lose their original form and position. The progressive changes make it difficult to recognize the original location in many specimens on account of deformity and the scarring of the duodenum. A thorough microscopic examination of the removed part of the duodenum would be interesting and perhaps more convincing as to the nature and location of these lesions.

The characteristic localization of these ulcers in the same segment and on the anterior and posterior walls, opposite each other, is significant. A few of these ulcers were observed by myself in the experiments where the muscle of the jejunum was stripped, had the appearance of the "kissing ulcers" of the duodenum in the human (Fig. 4) and were found in the same circular segment of the jejunum (Fig. 3). It has been pointed out in several previous communications that these ulcers were at the segment of the jejunum where the muscle layer began its normal intact course, and exactly ten centimeters distal to the propelling force of the pylorus (Steinberg; Steinberg and Starr) (10). A mechanical trauma as of etiological importance can therefore definitely be excluded.

The experimental and clinical evidence, particularly as it concerns the localization of duodenal ulcers and jejunal ulcers, is suggestive of a certain theory of a local mechanism. While the search for some dominant cause in the diencephalon, or in some endocrin imbalance, or both, is highly interesting, it does not explain the typical location of many of these ulcers. So far there is no conclusive evidence of a definite pathological condition existing in the brain of individuals suffering from peptic ulcerations. Periodicity of the symptom complex in itself would make some pretense of a denial that there is a continuous pathological process in the diencephalon. One is therefore hardly justified to go farther than the observation that hypersecretion, hypermotility and hypertonicity of the stomach are closely related to the ulcer symptom complex and that these conditions are frequently found in the young type of individuals. It may also be stated that the ulcer symptom complex is frequently initiated in an environment of strain, worry and other forms of mental upsets.

Ulcers do not occur in the duodenum or jejunum because the complicated nervous mechanism which controls the motility, secretion and blood supply are constantly found in a certain equilibrium. These three factors are closely related to each other and influenced by the nervous system. A disturbance of one com-



Fig. 4. Distal two-thirds of a stomach recently removed by the Author. "Kissing ulcers" in the duodenum which in their form and location closely resemble the experimental "kissing ulcers" in Fig. 3.

SECTION III—*Nutrition*

The Chemical Nature of the Anti-Anemic Principle*

By

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THE chemical nature of any physiologically active substance is of particular interest to the biological chemist in that it leads to the determination of the structure of the reactive material. And the work of the biological chemist will not have been completed before he has related the structure of such material to its physiological reaction (40).

Before the chemical nature of any substance can be accurately studied, its isolation in a pure state is of prime importance. In truth, however, a review of the literature offers rather discouraging results in this respect; for no one has laid claim to the chemical individuality of any product yet prepared. Nevertheless, enough negative proof has been offered to serve as a basis for much speculation, which, though doubted even by its own author, provides a working ground for further investigation.

The work on the isolation of the active principle was begun after Minot and Murphy (1), induced by the provocative work of Whipple (2), showed that liver was a rich source of anti-anemic principle.

Before entering into the discussion of this principle, it is important first to obtain a conception of the exact physiological reaction produced by the factor, that is indicative of its presence in a product.

A small percentage (1% in normal adult) of the circulating blood cells contain a material that shows a bluish net work when stained with brilliant cresyl blue. Because of this property these cells have been called reticulocytes. The reticulocytes arise from the bone marrow and eventually become red blood cells (3).

It is the remarkable increase in the number of these cells as effected by the anti-anemic principle that has been the basis for determining the presence of the factor in its various sources. Figure 1 shows a typical reticulocytic response.

Castle and Minot (3) have recently described and interpreted this reticulocytic response to anti-anemic material. Their study is at this time especially important because of the need of a more quantitative basis of evaluating products said to be capable of such hematopoietic activity. Furthermore, the lack of a more available biological test makes it more necessary.

The first attempt at fractionation was systematically undertaken by Cohn and his collaborators (4). Such an investigation required a chemist to do the isolation work, a doctor and his technicians to study the responses, and above all, enough patients with pernicious anemia to test out the various products. Hence the first report was the work of E. J. Cohn, G. R. Minot, J. F. Fulton, H. F. Ulrichs, F. S. Sargeant and W. P. Murphy. And yet the product remains a mystery.

They proceeded finally as follows (5): fresh minced beef liver was directly made acid and filtered. The

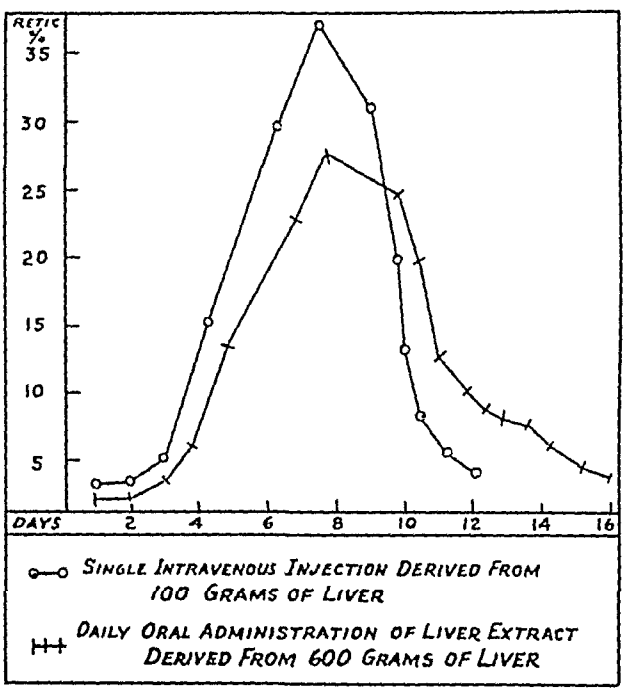


Fig. 1

filtrate (A) was heated and the coagulate proteins (C) separated. After the resulting solution (D) was concentrated, it was found to be clinically active. The potency was not diminished after extracting D with ether and 95% alcohol. The active residue remaining after the alcohol extraction was called G and was immediately put on the market as Eli Lilly's "343."

This fraction was further purified by precipitating the carbohydrates with an alkaline solution of lead acetate. After proving the filtrate, 0, to be active, it

*From the Division of Biologic Chemistry, University of Michigan. Submitted April 6, 1936.

ponent influences the others. Clinically it is seen that there are definite cycles, crises and stimuli which are demonstrated in the functional disturbance of the stomach which finally lead to the formation of ulcer (Kalk) (6). Nor can one underestimate the importance of the equilibrium which also exists between the acid stomach and the alkaline duodenum or jejunum after a gastro-enterostomy. A gastro-intestinal anastomosis mobilizes the compensatory forces in order to maintain the necessary equilibrium between the stomach and jejunum. Under adverse conditions when the acidity of the stomach contents are abnormally high a jejunal ulcer or jejunitis takes place.

From the experimental work and clinical evidence there is sufficient support to consider hyperacidity, hypersecretion and spasm as a vicious circle. At times it is difficult to differentiate an acid gastritis or duodenitis from a duodenal ulcer. In fact a typical ulcer symptom complex may be present in the absence of a duodenal ulcer. A patient with a hyperirritable acid stomach under certain conditions is a candidate for a duodenal ulcer.

It is impossible to bring within the limits of a short paper the numerous theories advanced, or give credit to the important experimental work or to introduce much of the controversial material. Only factors under experimental control which closely parallel the clinical picture have been emphasized. It is because of these considerations that the gastric ulcer was left out, since thus far it does not seem to fit into this picture.

The experimental ulcers of the jejunum are produced with such ease by varying certain anatomical relationships between the stomach and the jejunum, based on the expected physiological changes, that a conception of the nature of these ulcerations becomes fully tangible (Steinberg and Proffitt).

A familiarity of these principles enables us to proceed "mutatis mutandis" with a rational medical and surgical treatment.

SUMMARY

In addition to a previous communication, ten more dogs were operated on according to the Exalto method and with the muscle of the jejunum stripped for an area of ten centimeters. Again, no ulcer took place where the muscles were stripped. In ten dogs operated on in this manner one ulcer was found one or two millimeters distal to the gastrojejunal anastomosis. In three dogs ulcers were found ten centimeters distal to the gastrojejunal anastomosis or exactly where the muscle area began its normal course. This interesting observation, reported elsewhere for the first time by the Author in another series of experiments, appears highly intriguing.

The progress of a sponge through a Thiry-Vella loop is definitely delayed when the sponge is immersed in hydrochloric acid ranging from 0.15 per cent to 0.3 per cent. The experiments with the Thiry-Vella loop are supportive of our previous contention that there is a close relationship between acidity and spasm of the jejunum and the etiology of the experimental ulcerations.

Emphasis is made upon the experiments of gastro-intestinal anastomosis which are in a greater part a replica of surgical procedures used in the treatment of peptic ulcerations. The typical jejunal ulcerations closely resemble the duodenal and postoperative ulcerations in the human.

No denial is made of the importance of the vegetative nervous system (diencephalon), and the endocrin glands or the constitutional type.

Emphasis has been made upon the equilibrium which normally exists between the stomach and duodenum and which may be disturbed in the individual with a certain constitutional predisposition and in an unfavorable environment. This initiates a local vicious circle of acid and spasm between the stomach and the duodenum or the jejunum in a gastro-enterostomy.

It is far from my intention to give these experiments and reflections a pretense of completeness and finality. It serves only to emphasize an interesting experimental observation and an attempt to explain the part which the local mechanism of the ulcer symptom complex plays as related to a general conception, as yet less tangible and so far experimentally, without conclusive evidence.

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phuric acid with mercuric sulphate in presence of alcohol and ether.

Carbohydrates were considered to have been eliminated by Cohn, Minot and Murphy (9, 10) by the precipitation with lead acetate, after which the solution gave a negative Molish. Sturgis, *et al*, found that glucosamine could not be present because it would be held back by permutit, through which the material containing the active principle had been passed. No investigators have intimated the possibility of the anti-anemic principle's containing carbohydrate except Dakin, whose work will be taken up in detail later.

Figure IV

COMPOSITION OF S ME COMMERCIAL LIVER EXTRACTS

A Kapneler-Adler and A Lutsada (7)

		Peptone-ein 22 evap	Campolon C	Fermae-am C evap	Liver Ex. 343
Tot - N		100	100	100	100
Basic - N		48 16	47 69	59.85	64.86
Fraction One					
Phospho-Tungstate Ppt	Albumins Nucleoprotein-N	15 72	12 48	12.26	20.61
	NH_2-N	15.04	38.93	19.71	35 50
	Purine - N	79	2 17	3.65	
	Creatinine - "	1.53	41	2.76	3.05
	Basic Ppt - N	11.72	-	10.49	3.70
Fraction Two					
	Creatine - N	-	-	-	-
Filtrate	Urea - N	-	-	-	-
	NH_2 acid - N	7.99	8.19	20.20	21.57
	Polypeptid	21 14	35.03	10.25	2.83
	Undet Ppt. - N	22.71	7.09	9.70	11.24
f	11	6	6	6	6

By the method of Fürth and Schwartz (8) these investigators found that the extracts could be divided into two parts with phosphotungstic acid:

1. Precipitated by phosphotungstic acid
2. Not precipitated by phosphotungstic acid

Because no ether liver extracts have shown any anti-anemic potency, everyone is in agreement that the principle is not lipid in nature.

The possibility of purine bases, polypeptids and nitrogenous base were considered by Cohn and his collaborators (10). Because an active solution gave no precipitate with trichloroacetic acid, or tungstic acid, no increase in amino nitrogen on hydrolysis and no biuret reaction, they discarded the possibility of it being a polypeptid. Felix and Frühwein (13) also came to this conclusion, as did Reiman, *et al*, (35).

Although slightly soluble in 95% alcohol, the active material, regenerated from phosphotungstates, has been dissolved in it (10) and found active. The undissolved proteoses, peptones, and polypeptids were inactive. On further concentration with alcohol, active material was precipitated which contained largely nitrogenous bases.

Purine bases were removed and no precipitate was obtained with flavianic acid in neutral solution. That nitrogenous bases were still present was confirmed by the fact that the solution still gave precipitates with magnesium acetate.

The material precipitated from the alcohol, freed of protein, carbohydrates, lipids, proteoses, peptones and polypeptids which Cohn and his co-workers called "I.E." was the basis of all further investigations by this group (10).

With various mixtures of alcohol, water and ether, they succeeded in separating hematopoietically active fractions free of phosphorus, iron and sulphur compounds. In addition, it also gave negative Molish, biuret, Pettenffoffer, Millons, nitroprusside, and diacetyl reactions; furthermore, tryptophane, tryosine, arginine, cystine and creatine were absent. No precipitates were produced with trichloroacetic, picric, picrolanic or flavianic acids. However, it not only still gave precipitates with phosphotungstic acid and mercuric sulphate in acid solution, but also with gold and platinum chlorides and silver nitrate. Two grams of this substance produced a maximal reticulocytic response.

The final proof of the school of Cohn which led to confirmation by pure negative evidence that the active principle was of the nature of a nitrogenous base, was based on the following observation:

By treating the product just mentioned with ether and alcohol and later repeatedly recrystallizing it with mercuric sulphate, they removed a crystalline substance whose nitrogen was all alpha-amino-N. Formol titration showed that the carboxyl groups were equal in number to amino groups. But this crystalline substance was *inert* clinically.

Nevertheless, by extracting the precipitate containing mercury and the active principle with various mixtures of alcohol, ether and water, they succeeded in producing a product which no longer contained appreciable amounts of alpha-amino-N. It also showed no increase in carboxyl groups when treated with formaldehyde. This substance was highly potent.

Thus the inactive crystalline substance showed amino acid properties, but the active potent material showed no such properties; and as a conclusion the investigators claimed the active principle "gave strong evidence of being a nitrogenous base of the secondary or tertiary amine type." In addition, since the nitrogen in the purest fractions never exceeded 10.8%, purine and pyrimidine bases could be excluded, but not rings of the pyrrole or pyridine type.

At about this time (1930) Randolph West and Marion Howe (14) thought they had isolated the anti-anemic principle in crystalline form as the quinine salt of beta-hydroxyglutamic acid. It was precipitated from the acid hydrolysate of a product prepared as follows:

What remained of an aqueous solution of a commercial liver extract after it had been extracted in turn by saturated picric acid and a mixture of butyl alcohol and ether, was precipitated with fresh lead hydroxide, then with lead acetate; after removing the heavy metals, the solution was again precipitated with phosphotungstic acid with which the active material came down as the tungstate. Upon regeneration and removal of tungstate the solution was concentrated and precipitated with absolute alcohol. It was from the hydrolysate of this precipitate that hydroxyglutamic acid was isolated. Later Dakin and West (16) also isolated

hydroxyproline and concluded that the anti-anemic principle was made up of these two amino acids.

Still later, however, West and Howe withdrew their claim (17).

Here is seen the obvious necessity of a more practical test for active products.

In 1933 Felix and Frühwein (13) who have already been quoted, also found that the anti-anemic principle was not a peptid. Furthermore, they reported that no fraction less than 7% N was active and that their product gave them a negative biuret, a positive diazo, Sakaguchi and ninhydrin, but that they only obtained a positive Millons with mercuric sulphate precipitates. In further agreement with Cohn and his school, these workers found neither phosphorus nor sulphur. Reiman (35) and his co-workers had at this time found that the active principle in Heprakton was not broken down by the enzymes, erepsin, pepsin or trypsin, and concluded also that it must be of the nature of an amine rather than a polypeptid.

Joe Erdos has obtained a substance by digestion with sulphuric acid at various temperatures and subsequent purification which has a total nitrogen of 4.414% and shows on hydrolysis an increase in amino nitrogen of 300% (51). He prepared this as the silver salt whose molecular weight was determined as $C_{27}H_{72}N_{10}S_3P_2Ag_2$. But since he has used dogs to test the hematopoietic activity of his product, its relation to the antipernicious anemic factor is questionable; the more so because it has been shown that fractional parts of anti-anemic material may be active in animals, but that only the combination of the fractions is effective in humans (50).

COMPOSITION OF SILVER SALT

C —	78. %	Amino-N —	.86%
H —	7.2%	S —	.94%
O —	5.74%	P —	6.2%
N —	1.2%	Ag —	3.7%

He has calculated 18 amino acids from N content and believes there are three free carboxyl groups. His product gave a positive biuret and no precipitate with sulfosalycylic acid.

Before entering into the discussion of the most recent work on the anti-anemic principle, some insight as to its chemical nature may be obtained in reviewing the work on the physiology and pathology of the substance.

The most thorough review of this phase of pernicious anemia has been offered by Karl Singer (18) and Klumpp and Koletsky (19).

Work in this field was started by the brilliant investigation of W. B. Castle (20) on the relation between gastric secretion and pernicious anemia, which revealed "that in contrast to conditions within the stomach of the pernicious anemia patient, there is produced during digestion of beef muscle within the normal stomach some substance capable of promptly relieving anemia, similar in this respect to the substance found in liver." Following this discovery, he developed in a series of papers (21-23) a theory which runs as follows:

Because beef muscle and gastric juice are each ineffective as anti-anemic factors when fed to patients with pernicious anemia, and because, when previously allowed to interact and then fed, they are hemotopoietically active, there must be two factors that produce an anti-anemic principle that is related to the material found in the liver.

The one is an *extrinsic* factor present in beef muscle, and the other an *intrinsic* factor found in gastric juice. Thus:

EXTRINSIC FACTOR + INTRINSIC FACTOR = ANTI-ANEMIC PRODUCT

Castle's now classical *in vitro* synthesis of active principle consisted in heating raw beef muscle and fasting normal gastric juice and bringing the solution to the proper reaction with HCl.

According to Castle *et al* (21) the intrinsic factor is organic in nature, is destroyed when heated at temperatures between 70° and 80° for one-half hour, or 44.5° for four days, and that it is probably an enzyme.

Of the extrinsic factor he found that isoelectric precipitation (21) of beef muscle after extraction with ether produced a substance able to substitute for beef muscle. In addition, the fact that acid hydrolysis of liver extract until the anti-anemic factor was destroyed, does not destroy extrinsic factor; the fact that the substance in autolyzed yeast is capable of resisting autoclaving for five hours at fifteen pounds pressure; the fact that extrinsic factor is soluble in 80% alcohol and finally, the fact that it is present in leached casein, wheat glutelin and in animal or yeast nucleic acid, led Castle and Strauss (24) to suggest Vitamin B_2 as the extrinsic factor. However, as the literature began to fill up with reports disproving this, Castle himself (25) doubted the relation. Among the first to report these results were Wills (26), Lassen and Lassen (28) and Dühl and Kühnau (27). Wills (26) showed that Vitamin B_2 (of egg white) incubated with gastric juice was inactive hematopoietically. Recently Vitamin C has been found to be absent in an active product (38).

In 1932 Klein and Wilkinson undertook the study of the extrinsic and intrinsic factors and after a series of investigations (29-32), they finally concluded that the intrinsic factor was an enzyme (32) which they had named "hemopoietin" (29); and that the substance produced by the action of this enzyme on extrinsic factor was the same as the active principle found in liver. They then wrote the reaction:

ENZYME + SUBSTRATE = PRODUCT or
HEMOPOIETIN + EXTRINSIC FACTOR
ACTIVE PRINCIPLE IN LIVER

In these investigations Klein and Wilkinson first found that hemopoietin could not be extracted from stomachs by methods used to isolate active material from liver; second, that it came down with the protein fractions when precipitated from alcohol; and third, that it was heat labile. Because of these observations they decided it was entirely different in nature from the active principle in liver and changed their methods of isolation accordingly (29).

Hence, they used a special high compression apparatus (29) to express the juice of stomach tissue.

On adding alcohol to an acid solution of the expressed juice, a precipitate was obtained which contained hemopoietin and pepsin. The filtrate contained neither of these and was clinically inactive. On treating the precipitate with .1N HCl to a pH-2, it was found that the activity of hemopoietin was destroyed but peptic activity remained. Adding acetone to the .1N HCl solution also inactivated hemopoietin. But when the

acid solution was brought to pH 6.2 and precipitated with alcohol, the precipitate, though it was practically free of pepsin, was hemopoietically active.

The significance of this preparation lies in the fact that the gastric juice factor had been proven to be both different in nature to pepsin and independent of pepsin in its action.

By virtue of this preparation and further study, Klein and Wilkinson showed hemopoietin to be enzymic in nature. They listed the following reasons (32):

a. Expressed from gastric juice.
b. Invariable association of pernicious anemia with deficient enzyme secretion.
c. Difficulty of extraction of hemopoietin from tissues.
d. Its apparent destruction by prolonged action of pepsin and trypsin.
e. Its association with the protein fraction of stomach press juice.
f. Its thermolability and sensitivity to chemical treatment.
g. Its instability.
h. The fact that the reaction of a thermolabile substance on a substrate produced a thermostable substance. At the same time they tried to show that the product of this enzyme reaction was the same as the active principle in liver. The following tabulation best summarizes their results:

TABLE—Klein and Wilkinson (32)

Hemopoietin	Active principle in liver	Product of hemopoietin and beef
1. ppt. with proteins	not ppt. with proteins	not ppt. with proteins
2. positive protein reactions	negative protein color reactions	negative protein color reactions
3. Soluble in water	Soluble in 70% alcohol	Soluble in 70% alcohol
Insoluble in 70% alcohol	Soluble in 70% alcohol	Soluble in 70% alcohol
Thermolabile	Thermostable	Thermostable
Inactivated by acetone	Unaffected by acetone	Unaffected by acetone

As fine as these relations look, Castle (25) claims that since these authors prepared their product of enzyme digestion of beef muscle at a temperature of 37.5° and then only heated to 60-65°, they had no right to claim its thermostability equal to that of the anti-anemic principle in liver. He stated that active principle in liver is inactivated by heat only after:

1. Boiling for 5 minutes.
2. Heating to 10-80° for ½ hour, or
3. 40° for 3 days.

Castle, however, believes that Wilkinson and Klein may have been studying a precursor of the active principle (25). This equation would be:

HEMOPOIETIN + EXTRINSIC FACTOR = PRECURSOR TO ACTIVE PRINCIPLE

In support of their enzyme hypothesis Klein and Wilkinson cited the work of Helmer, Foutes and Zerfas (33).

After ultra-filtering gastric juice these investigators found that both filtrate and residue were inactive. But if the gastric juice were concentrated *in vacuo* it was found to contain anti-anemic activity. Also, when this concentrated gastric juice was ultrafiltrated, the material unable to pass through the filter was found to be inactive while the filtrate contained a substance capable of producing a reticulocytic response. In addition, the part of *fresh gastric juice* unable to pass through the ultrafilter was concentrated *in vacuo*, and it was found to contain the active principle, while the same treatment of the filtrate failed to produce active product.

The significance of this experiment may be seen more easily in the following diagram:

FRESH GASTRIC JUICE

Ultra-Filtered		*Concentrated in Vacuo (Active)*	
Residue (Inactive)	Filtrate (Inactive)	Ultra-Filtered Residue Inert	Filtrate Active
Concentrated in Vacuo	*Concentrated in Vacuo*		
Product is Active	Product Inactive		

To explain the part of this picture that strengthens the enzyme theory:

H = enzyme
B = substrate
A = active principle

Filtrate thus inactive in concentration

Conclusion:

H + B (Large molecule) *concentrated in vacuo* = A (Small molecule)

Greenspon has recently offered an entirely different conception from that of Castle and of Wilkinson and Klein. He believes that the external factor is not a source of potentially active anti-anemic substance, but that it is merely effective in blocking the antagonistic action of pepsin on the active principle in the gastric juice (45). Thus:

anti-anemic principle + pepsin + protein gastric juice (Inactive) = anti-anemic principle (Active) + protein-pepsin complex

In support of his view he showed that pepsinized ventriculin and pepsinized gastric juice are each ineffective, but when these substances are not subjected to the action of pepsin they are clinically active. On this basis and on the basis of the protein's absorbing the pepsin, he re-interpreted Castle's experiments and the action of the stomach extract. The work of Wilkinson and Klein (29, 30) he refuted by saying that the differences in thermolability between the stomach "enzyme" and liver principle are due merely to the impurities in their mixtures. Greenspon, thus, does not believe that the stomach and liver principles are different. As stated above, Castle did not believe that Klein and Wilkinson were dealing with the anti-anemic principle of the liver, but he did believe that it might be a precursor. Finally, Dr. Greenspon failed to explain the experiments of Foutes, Helmer and Zerfas which Klein and Wilkinson had used to support their hypothesis.

This question of whether the principle of gastric juice is itself the anti-anemic principle, whether it is a hormone (46) or whether it is an enzyme can only

be definitely settled by determining the exact chemical constitution of the anti-anemic principle.

This leads us to the work of Dakin whose speculative conclusions, though based on negative experimental results, now become increasingly more significant.

One does not have to go far off the trail of the work done on the active principle of pernicious anemia to trace back the possible steps that reviewers in the future may use to show how Dakin may have arrived at his speculation. I am presenting this both to make it easier to appreciate Dakin's work and to see some positive truth in his negative results.

After Minot in 1926 pointed to the liver as a source of the anti-anemic principle, Castle in 1929 brought our attention to an activity in the stomach as a step in its production. By 1933, Sturgis and Isaacs (37) had produced a desiccated stomach preparation containing the anti-anemic principle. In 1934, Wilkinson and Klein (32) showed that gastric mucosa was also a source of an anti-anemic principle. In addition, Helmer, Foutes and Zerfas (33) had shown that gastric juice contained both the supposed enzyme and a potentially active material.

And now the work of Dakin has led him to the point of saying, "It is obvious that a substance of the chemical nature (hexosamine polypeptid) of the substance under question (active principle) might well be considered as having intimate relation with a rather indefinite group of substances classified as mucins . . ."

Since his is the most recent work on the subject and dares to go further than any other work so far presented on the chemical nature of the anti-anemic principle, it will be of interest to see exactly how Dakin, on purely negative evidence, led up to the belief that glucosamine, a possible breakdown product of a hypothetical stomach mucin, may be the structural unit of the anti-anemic principle. It must be remembered that Dakin (6) lays no claim to chemical individuality of any of his products.

All of the following is from Dakin and West (6):

The product studied was that obtained by repeated salting out with magnesium sulphate of active material purified with alcoholic calcium acetate, Reinecke's acid, and repeated salting out with ammonium sulphate. Its analysis is as follows:

	Percent
Carbon	50. -51.4
Hydrogen	7.0- 7.2
Nitrogen	15.2-15.4
Amino Nitrogen (Van Slyke)	.4- .5
Amino Nitrogen (after hydrolysis)	10.6-10.8
Sp. Rotation in Degrees	95 - 106

After hydrolysis the amino nitrogen increased more than twenty-fold.

Amino Acids Present After Hydrolysis

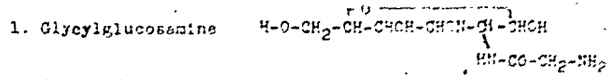
Histidine	.1 (trace)
Arginine	14
Lysine	5
Leucine	15
Hydroxyproline	10-14
A monoaminodicarboxylic acid fraction as Ca salts	41-45
50% of which Aspartic acid	
5% of which Glycine	
15% of which Aminohexose	

From the hydrolysate there was obtained an aminohexose which appeared to be like glucosamine rather than the isomeric forms, isoglucosamine or fructazine because:

1. It gave a phenylglucosazine on treatment with phenylhydrazine.
2. It formed pyrrole derivatives on condensation with acetyl acetone, which is the basis of the quantitative method for glucosamine.
3. Ammonia was liberated in treatment with alkali, which is characteristic of the glucosamine type of compounds. And chondrosamine was absent.

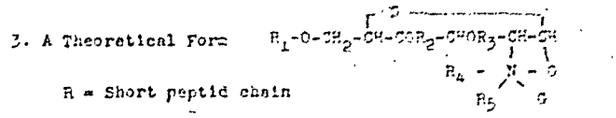
Though the product gave a positive Molish reaction, Dakin found that glucosamine polypeptids behave similarly. An atypical biuret like that of the product was obtained by synthetic glucosamine. He offered three possible types of structures to the glucosamine.

1. Glycylglucosamine



2. Anhydride Form

3. A Theoretical Form



R = Short peptid chain

Properties	NH_2N	Fehlinge	Biuret	OH groups
1.	50%	x	?	many
2.	0	-	green	many
3	0		?	none
4. Active product	(very little due to arginine)	-	green	many

Because of this relation the anhydride was assigned to the possible chemical structure of the active principle.

Laying grounds for future investigation Dakin discussed the possibility of the polymerization of the hexosamine; that is a proteose, peptone or polysaccharides.

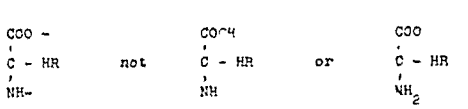
"Whether the aminohexose is united in polysaccharide form as the chitobiose obtained from chitin by Bergmann, Zerfas and Silberkeit (34) remains unsolved. Preliminary experiments have shown that acetolysis of the substance gives unsatisfactory results because while an acytated compound readily soluble in chloroform is obtained, there are still groups attached to the glucosamine skeleton."

Because it is not precipitated by trichloroacetic acid, ferrocyanic and, or rufianic acid, but is precipitated by tannic acid, it would be classed as a peptone. But because it is easily salted out by $(NH_4)_2SO_4$ makes it a proteose. However, by using synthetic products again, he claimed that peptids of three or four amino groups are known which can be easily salted out, thus "making this distinction arbitrary."

In addition Dakin obtained a red color with alkaline picric acid which indicates the diketopiperazine group, but since glucosamine gives precisely the same reaction, he believed the test to be "within value under the circumstances."

He claimed also that a positive diazo Pauly reaction obtained from a virtually free histidine product was due to glucosamine. Finally, complete inactivation was brought about by boiling with $(NH_4)_2SO_4$. "This can be expected of a substance like a glucosamine poly-

peptid." As for the other chemical properties, he found that action of cold alkali brought about complete racemation of amino acid groups, as well as a marked reduction in specific rotation of reactive product. As a result he assigned the internally bound forms to alpha amino and adjacent carboxyl group. Thus:



These results, as negative as they are, do point to the active principle being a polymer with a glucosamine unit, even though glucosamine has itself not been isolated. Its isolation would certainly be welcomed.

The more definite work of Dakin consisted in showing the molecular weight to be a multiple of 570 by the percentage Reineckate, of 1430 by titratable acidity, or of 2920 by percentage of lysine. Moreover, he found that it can be decomposed by pepsin and erepsin and showed the absence of purine and pyrimidine bases. Reiman, Senek and Fritsch (35) claimed that their active material was not attacked by pepsin, trypsin, or erepsin. It may be that they did not permit it to act long enough; for on comparison of the data with Dakin's, we see that the German workers only let their enzyme act for 48 hours (Fig. 4).

It is not hard to see how this work of Dakin's is entirely out of harmony with the work done before 1935. For instance, Cohn and his school, it should be recalled, obtained precipitates with picric, picrolonic, and flavianic acids while Dakin did not; and that Cohn got a negative biuret, negative Molish, and negative diacetyl reactions. Furthermore, Cohn and his associates, Felix and Frühwein and Reiman (*et al*) were rather certain the anti-anemic principle was not peptid in nature.

SUMMARY

To summarize the work done, all that can be said is that before 1935, most of the sentiment rested with the anti-anemic principle's being a nitrogenous base while Dakin has since shown us the possibility of a glucosamine peptid perhaps derived from a mucin-like substance.

Further work on the chemical nature of the anti-anemic principle, greatly retarded by the present methods of testing products, will surely go ahead much faster should a more convenient method be developed. In this respect K. Singer has recently suggested the use of rats (36). In addition, after making a complete survey of the literature on the bioassay of anti-anemic material, Jacobson (47) has himself offered a guinea pig technique (48) which proved to be most promising. Crude extracts of fresh human livers assayed by him yielded results that corresponded beautifully with the state of the patient in pernicious anemia. However, his work has not yet been confirmed and some who have tried it deny its usefulness (49).

NOTE: The author is aware of the work recently done on the hematopoietic action of phosphoric acid compounds of creatine and creatinin by U. Syzuki, W. Hakahara and F. Inukai; however, since this work was done on rabbits we cannot use it as such in discussing the chemical nature of *anti-anemic principle* (39).

Figure V

I. DAKIN—EREPSIN DIGESTION (6)

Substrate (product discussed) = .45 gm. (containing 67.5 mg. of N)

Total volume = 50 c.c.
Temperature = 35°
Increase in NH_2-N (Van Slyke)

	Blank mg.	Substrate mg.
4 hours	0	6.6
1 day	3.9	9.9
4 days	8.1	26.7
10 days	8.4	36.0
20 days	9.0	43.2

II. REIMAN (35)

3 gm. Heprakton
3 Erepsin units

Hours	Mg.
0	4.676
1	4.814
2	4.701
3	4.701
24	4.780
48	4.914

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SECTION IV—*Roentgenology*

Functional Changes of the Vermiform Appendix Producing Diverticular Sacculation of the Spastically Contracted Organ

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THE case reported here represents an unusual functional anomaly of the vermiform appendix, as evidenced and demonstrated by means of its Roentgenological aspect. The functional changes as exhibited on the films, are not permanent, nor uniform; they are rather shifty in character. The appendiceal picture is unusual, somewhat grotesque, as regards its morphological appearance. Although the films are not alike, nevertheless two characteristics are readily demonstrable on each of them, viz.: a *spastic contraction* of some and a *circumscribed dilatation* of other segments of the appendicular lumen. These constituents, alternating over the various segments, are readily discernible on each of the films.

In the properly exposed right iliac fossa, the vermiform appendix is well visualized with a narrow, spastically contracted, nearly obliterated lumen. The configuration and position of the appendix vary on the different exposures, proving a free moveability and contractility, i.e. a proper physiological behaviour. From a pea to a bean sized sacculation, a diverticular or cyst-like sudden expansion of the lumen was demonstrated on each of the films. The size, the location and the shape of the sacculation were not strictly uniform. It was located on some of the films closer to the proximal, on some others again closer to the distal end of that organ and extended in different directions, on some of the exposures upward, on others again, downward or along the course of the lumen.

CASE REPORT

A. S., 32 years of age, white, female, singer, first seen at my office on the 11th of December, 1928. The chief complaints referred to certain abdominal pain, with a localization in the left upper quadrant. Painful attacks recurred at gradually increasing frequency, in intervals, since the last five years. In the early stage painful periods were followed by 8 or 9 months' free intervals, in contrast to the more recent state when painful and free periods alternated with each other in nearly equal time intervals (2 or 3 weeks). Patient was during the first examination for five days in the midst of a painful period. The pain, as described, was rather sharp, continuous, still never severe enough to confine patient to bed. Maximal pain occurred a few hours after meals. Before and immediately after meals patient felt relatively free. Other data of history were of no significance.

Within her memory, patient has felt very nervous, a condition, which has been aggravated since the onset of the present ailment. She felt trembling in her body, especially during painful abdominal attacks, and was highly irritable, tense.

The physical examination revealed a circumscribed tender area above the umbilical region, over the left side, below the splenic flexure, the tender area being of a higher location than encountered in gastric ulcers. The appendicular, the gall bladder, and the pyloric regions failed to show pressure tenderness or other signs of any pathology.

X-ray examination of the gastro-intestinal tract revealed a perfectly normal stomach and duodenum. No direct or indirect signs, or even suggestive symptoms of a peptic ulcer were detected. The descending colon showed a very marked spasm, throughout its length, the contracted lumen being even narrower than an average appendicular lumen. No transverse rugal or haustral markings were visible. The appendix showed spastic contraction with diverticular sacculation of its center, as above mentioned. On repeated examination, the spasm in the colon changed, with a simultaneous shift in the appendicular configuration. After a few months' rest, combined with psychic and medical treatment, condition of the patient improved to a great extent, pain had disappeared entirely and in this improved mental and physical state, a re-examination performed, revealed an appendix, perfectly normal in every respect, with a uniform and equally patent lumen, without any sign of spasm or sacculation. The colon was similarly normal.

Patient, after years, has been in good health.

THE SPASM: ITS SIGNIFICANCE

The complaints, especially the post-cibal, left-sided, circumscribed pain were grossly suggestive of a peptic ulcer of the stomach. Closer examination and the X-ray study, however, were not corroborative. "Mucous

Submitted January 6, 1936.
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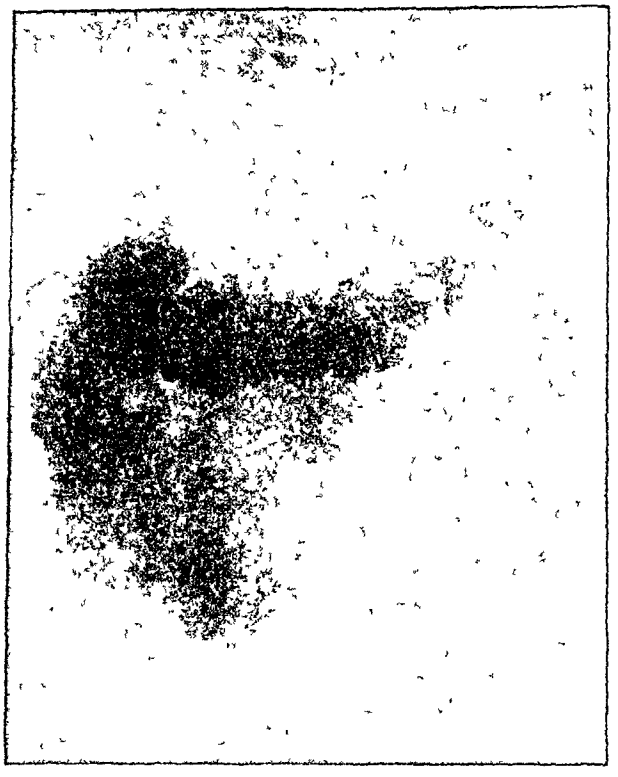


Fig. 1. Spasm of the descending colon. Observation during painful period.

colitis" (more properly "mucous colic") is well known to cause similar complaints, clinical symptoms and X-ray findings.

The neurotic constitution has or may have among many other symptoms, an "irritable colon" (Bargen); if this is associated with a certain type of "secretory" disorder, the case may resemble or be a "colica mucosa"; if however not the mucus-secretion is the predominant factor, the case can not be termed any longer colica mucosa, although the irritable colon with the "string-sign," with a similar or only slightly different clinical manifestation, may still equally be present. Consequently, the "string-sign" or the X-ray demonstration of a maximally contracted, spastic colon, is not pathognomonic in its significance: it is present in *neurotics, with or without colica mucosa.*

Still another aspect of the colospasm may deserve our fullest attention, because it is important from the practical point of view, i.e. that it may occur in the most varied morbid conditions, *also without the symptoms of any neurosis.*

In my experience—in accordance with the scattered references from the literature—similar spastic contractions over the colon may be encountered in certain cases, *without* any manifestation of a neurosis, merely as *reflex* or *secondary* concomitant symptom, at a primarily existing somatic condition in the abdominal cavity (appendicitis acuta, or chronica, cholelithiasis, peptic ulcer, carcinoma somewhere in the abdomen, etc.)

REVIEW OF LITERATURE

Concerning *spasm in the appendix*, insofar as it came to my attention in my search through the literature, there was no record of any paper dealing with, or of any X-ray film, demonstrating its existence. There are, however, occasional reports in the literature, referring to a "reversed mechanism," viz. when spasm in the alimentary canal was noted as a secondary manifestation, at a primarily existing appendicitis (Piccinino, Cristofanetti, Rendich and Ehrenpreis, Bordoni, etc.). Carman, Assmann, Meyer, Stierlin, Schlesinger, Jordan, etc., make very cursory or no references to spasms in the gastro-intestinal canal altogether, and none in the appendix.

In atrophic appendicitis the lumen is narrow, constantly, uniformly, throughout, with regular contour.

A similarly unusual feature is demonstrated by the presence of the *diverticulum-like sacculation* of the appendicular lumen.

On "prima facie" one might have diagnosed in my case a diverticulum of the appendix Such is a well established pathological entity, though rare.

True or congenital diverticulum of the appendix—an offshoot or cul de sac, often larger than the cavity of the viscus (Royster) was reported by Hedinger, Sissojeff, Jackemont, Stuerm, Gullotta, Malone, Lorrain, Martini and Rouffiac (literature see Royster, also Gullotta).

False or acquired diverticulosis has a somewhat higher incidence; two or three score cases have been observed in all (Lit.: Gullotta).

The acquired type of diverticulosis is usually classified as inflammatory or non-inflammatory. The rarer non-inflammatory type develops along the mesenteriolic attachment In the inflammatory type the diverticula may develop in any site, size or number. Ashoff's intramural abscesses frequently found in acute appendicitis, serve, regardless of their later outcome, into healing, with absorption and retraction, or perforation into a preformed peritoneal sac or into the appendiceal cavity—as a basis for a potential development of this type of acquired diverticulosis. It is generally assumed that as pre-requisite for the development of a false diverticulum, an increased intra-appendicular pressure is necessary, which in turn, is furnished as a result either of an inflammatory exudation, during an inflammation, or of a stricture, the result of past attacks, at the proximal lumen.

Cysts or cyst-like tumors of the appendix were in extremely rare cases likewise observed (Bachlechner, Oudard, Ribbert, Cameron).

The appendicular distention due to stasis (Jordan) represents a uniform, not cyst-like distention of the lumen.

COMMENT

The question to decide was, whether we are dealing here with an *anatomical diverticulum* or with the above mentioned *functional derangement?*

My reasons for assuming the functional character of this disorder seems to me to be substantiated for the following reasons: 1, the morphological picture of the appendix is dissimilar, in contrast to the anatomically fixed morphology as in the case of an organic disease; 2, other functional changes such as the spasm alongside the descending colon, co-ordinate the appendicular spasm to the colonic spasm; 3, the "experimentum crucis" is furnished by the fact, that at a time, after a physical improvement, and during a more relaxed state of mind, when no abdominal pain was complained

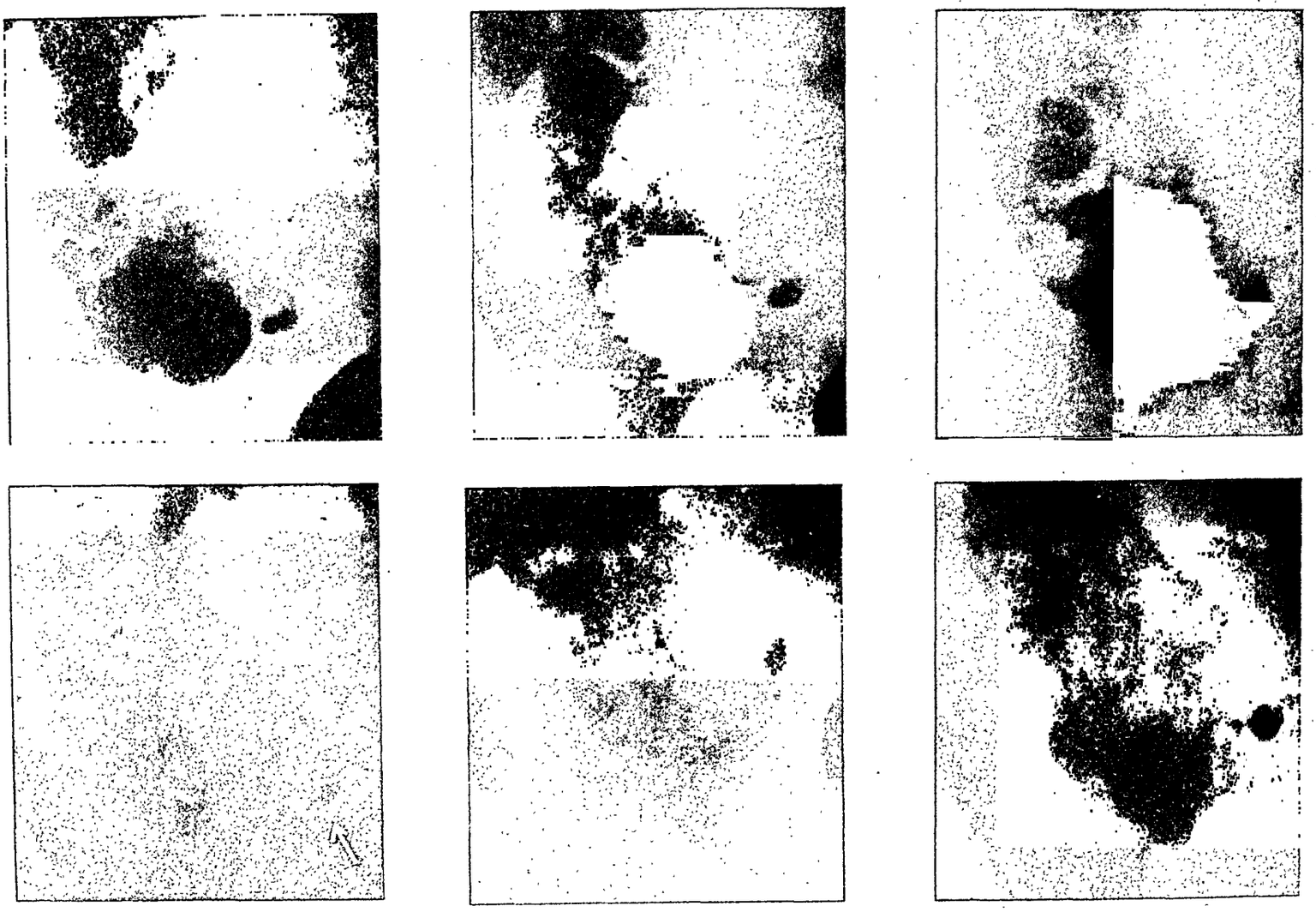


Fig. 2. Six films, taken at various intervals, 24, 31, 48 hours after barium meal, during painful period. Note size, site and location of the diverticular sacculation of the middle portion also the narrowed, spastically contracted both ends of the viscus. Spasm and sac shows shifty character to each other and to the surrounding tissues.

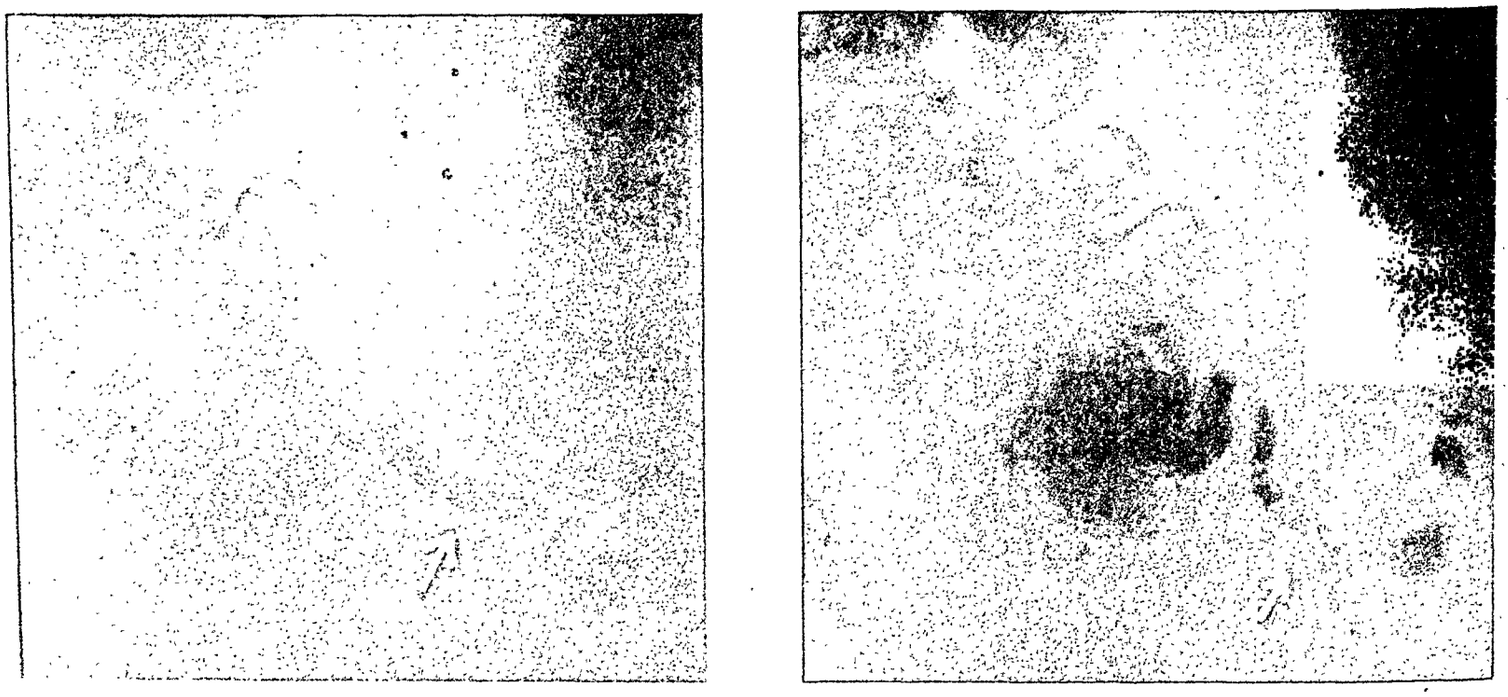


Fig. 3. Both films taken two months later, after improvement in health, in painless period. The appendix is freely movable. normal and uniform in contour, without any sign of sacculation or spasm.

of, the appendix, as demonstrated on the X-ray film, proved to be a perfectly normal appendix.

No further, or more convincing evidence could be procured by surgical or even by post-mortem inspection—both being unable to demonstrate functional changes, as roentgenological studies do.

The next question was, whether the spasm and the dilatation were merely incidentally observed together, or there might have existed some causal correlation between them.

Spasm over the colon does not produce compensatory dilatation proximally, in contrast to a narrowing, due to some organic lesion—a sign, valuable from the differential-diagnostic point of view. The shifty character and location of the spasm, furthermore the fact, that it is seldom fixed to the same site, for a longer period, may explain the failure of a compensatory hypertrophy, the first step to an organic dilatation.

Conditions in the appendix—in my case—were, however, slightly different. The partial spastic contraction squeezed the appendicular content from both ends into the relaxed middle portion. Should the proximal portion have failed to spastically contract, the appendicular content undoubtedly would have emptied into the cecum. Why just the two ends of the appendix were subjected to spasm, and not the entire length, cannot be stated. Against the assumption of any anatomical lesion, atresia, scar tissue, etc., as being responsible for this circumstance, served the fact, that at some later date, a perfectly uniform and smooth appendicular lumen was demonstrated. Against the possibility of a foreign body or a fecalith in the sac, militated the fact, that the cavity was *filled in* with the opaque material, and no external covering in form of a negative stone shadow was noted.

SUMMARY

Spasm of the descending colon co-existing with spasm of both, the proximal and the distal ends of the appendix was observed in a highly neurotic young adult.

Spasm along both ends of the appendix resulted in a diverticulum-like sacculation of the non-spastic, relaxed middle portion of the vermiform appendix, a morphological appearance hitherto often not described.

The characteristic X-ray picture as observed during the painful period, with a complete restoration to normal, in a free interval, prove conclusively, that the changes described were purely of functional origin.

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SECTION V—*Therapeutics*

III. The Rate of Absorption of Salicylates and the Effect of Certain Compounds on the Rate of Absorption of Acetylsalicylic Acid from the Stomach and Intestine*

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QUANTITATIVE determinations of the rates of gastric and intestinal absorption of salicylic acid and some of its salts are presented in this paper. In addition, the influence of certain compounds, which are used as "protectives" against the gastro-intestinal irritation caused by salicylates, on the absorption of acetylsalicylic acid has been studied.

Burow (1), Brequet (2), Houghton (3), and Delhougne (4) have reported observations on the absorption of salicylates from the stomach. These investigators, strictly speaking, did not study absorption from the stomach alone. Brequet ligated the pylorus

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TABLE I

Gastric absorption of salicylates in the anesthetized dog (Time 1 hr.)

Drug	Dog 1	Dog 2	Dog 3	Dog 4	Avg.
Acetylsalicylic acid	54.6%	45.7%	46.4%*	48.2%*	48.7%
Acetylsalicylic acid with calcium gluconate	51.0%	46.8%	47.1%	48.4%*	48.3%
Acetylsalicylic acid with 1000 mg. $NaHCO_3$	25.8%	29.6%	21.7%		25.7%
Acetylsalicylic acid with 500 mg. $NaHCO_3$	24.7%				24.7%
Acetylsalicylic acid with 250 mg. $NaHCO_3$	36.6% +				36.6%
Acetylsalicylic acid in 0.2% HCl	58.1%*				58.1%
Acetylsalicylic acid in 0.4% HCl	57.1%*				57.1%
Acetylsalicylic acid with MgO	17.5%	20.2%	19.2%†		19.0%
Salicylic acid	61.7%	62.9%	64.9%	67.1%	63.9%
Calcium salicylate	53.1%	44.3%	43.1%	47.5%*	47.1%
Sodium salicylate	14.7%	13.7%	11.6%		13.3%

*Positive ferric chloride test for salicylates in urine in 10-15 min.
+Positive ferric chloride test for salicylates in urine in 20-30 min.
†Positive ferric chloride test for salicylates in urine in 45-55 min.

TABLE II

Absorption of acetylsalicylic acid from the pouch of the entire stomach in the unanesthetized dog

% absorbed in 1 hour	% of absorbed acetylsalicylic acid recovered in urine
66.6%	
63.0%	
73.5%	66.9%
70.7%	66.2%
Av. 68.6%	

of the stomach in rabbits and guinea pigs and fed the drug by mouth. Delhougne produced a pylorospasm by introducing a drop of HCl into the duodenum of dogs with a chronic duodenal fistula and also fed the drug by mouth. None of these studies were quantitative; absorption was indicated by the salicyl-ferric-chloride reaction on the urine.

Pinczower (5) gave salicyl compounds orally to normal human subjects and found no differences in the rate of absorption as shown by the time of appearance in the urine. Blume and Nohara (6) determined the comparative rates of absorption of sodium salicylate upon oral and rectal administration, making quantitative analyses of both the blood and urine for salicylates at various time intervals. Following oral and rectal administration, they found traces of salicylate in the blood within 1½-2 minutes, but the concentration following rectal administration reached a higher peak in a shorter time than when given orally.

METHODS

Gastric Absorption: Anesthetized and unanesthetized dogs were used. The occluded stomach (ligature about the cardiac and pyloric orifices) of dogs under nembutal anesthesia was thoroughly washed with warm distilled water. The solutions under consideration were introduced through a glass cannula fastened by ligature in the pylorus and allowed to remain in the stomach for one hour. The residues were then washed into volumetric flasks, diluted to 500 c.c. and aliquots analyzed quantitatively for salicylates. In some cases the ureters were cannulated and diuresis established by intravenous injection of normal saline before the salicylate solution was introduced into the stomach. The urine so collected was analyzed qualitatively for salicylates with ferric chloride at five minute intervals.

In all cases 250 c.c. solutions containing 500 mg. of acetylsalicylic acid or its molecular equivalents, 383 mg. salicylic acid, 444 mg. sodium salicylate, 486 mg. calcium salicylate were used. The mixtures studied contained 500 mg. acetylsalicylic acid with either 1000 mg. sodium bicarbonate, 300 mg. calcium gluconate or 330 mg. magnesium oxide.

Gastric absorption in the unanesthetized dog was studied by one hour perfusions of 100 c.c. equi-molecular salicyl solutions through the pouch of the entire stomach (7). In some instances the urine was collected for several days

TABLE III

The effect of pH and molecular size upon the absorption of salicylates from the stomach and intestine

Drug	pH	Molecular Weight	% Gastric Abs. /hour	% Intestinal Abs. /0.5 hr.
Salicylic acid	2.5	138.05	63.9	59.4
Sodium salicylate	6.8	159.8	13.3	72.8
Calcium salicylate	6.1	350.18	47.1	58.3
Acetylsalicylic acid	2.9	180.06	48.9	17.1
Acetylsalicylic acid + Ca.-gluc.	3.5		48.3	50.7
Acetylsalicylic acid + $NaHCO_3$	7.3		27.7	14.4
Acetylsalicylic acid + MgO	9.0		19.0	17.9
Acetylsalicylic acid + HCl	1.7		58.1	
Acetylsalicylic acid + HCl	1.25		57.1	

after the perfusion and the amount of salicylate recovered determined.

Intestinal Absorption: Twenty-four inch, well-washed, but not traumatized, intestinal loops (upper ileum) of dogs under nembutal anesthesia were used. The solutions were introduced through a glass cannula and allowed to remain for 15, 30, 45, 60 and 75 minute periods. The residues were washed into volumetric flasks, diluted to 250 c.c. and analyzed for salicylates. In all cases 50 c.c. of solution containing 150 mg. acetylsalicylic acid or equivalent amounts of salicylic acid and its salts were used. The acetylsalicylic acid mixtures contained either 300 mg. sodium bicarbonate, 100 mg. calcium gluconate, or 100 mg. of magnesium oxide respectively.

Method for Determining Salicylates Quantitatively: Existing quantitative methods for salicylates were found inadequate. The method of steam distillation and subsequent ferric chloride determination of the salicylate as described by Thoburn and Hanzlik (8) was found unsatisfactory. The presence of large quantities of mucin, mucoid and other materials in the intestine which take up bromine excluded the direct application of the bromine titration method (9).

For these reasons a new method was developed. By determining the volume of carbon dioxide liberated by brominating salicylic acid in a Van Slyke apparatus, satisfactory results were obtained. Details of this method will be reported elsewhere (10).

TABLE IV

Hydrolysis of acetylsalicylic acid

Salicylate	pH of Sol.	Time	% hydrolysed
(1) Acetylsalicylic acid	1.76	2 hours	0.0+
		24 hours	0.0+
(2) Acetylsalicylic acid + Ca-gluconate	1.25	24 hours	0.0+
		2 hours	0.0+
	pH Buffer Sol.		
(3) Acetylsalicylic acid	8.25 8.0	2.5 hours	0.0+
(4) Acetylsalicylic acid + Ca-gluconate	8.25 8.0	2.5 hours	0.0+

TABLE V

Dialysis of salicylates through collodion sacs

Drug	%/1.5 hours
(1) Acetylsalicylic acid	58.0
(2) Acetylsalicylic acid + Ca-gluconate	60.2
(3) Acetylsalicylic acid + $NaHCO_3$	53.1
(4) Salicylic acid	55.7

RESULTS

Gastric Absorption: The relative rates of gastric absorption of the salicyl compounds and the mixtures studied are shown in Table I. Averages of data from four dogs for each solution show the following percentage absorption in one hour; salicylic acid 63.9%, sodium salicylate 43.3%, calcium salicylate 47.1%, acetylsalicylic acid 48.7%, acetylsalicylic acid and calcium gluconate 48.3%, acetylsalicylic acid and sodium bicarbonate 25.7%, acetylsalicylic acid and magnesium oxide 19.0% (Table I).

Perfusion of the total pouch of the stomach in the unanesthetized dog for one hour showed a slightly higher rate of absorption of acetylsalicylic acid (68.6%). Of the amount absorbed 66.9% was re-

TABLE VI

Intestinal absorption of salicylates at different time intervals in the dog

Time	Acetylsalicylic acid	Acetylsalicylic acid with calcium gluconate	Acetylsalicylic acid with $NaHCO_3$	Acetylsalicylic acid with MgO	Salicylic acid	Calcium salicylate	Sodium salicylate
15 min	21.2%	23.5%	17.7%		47.0%		41.3%
	16.4%	26.7%	15.3%		49.6%		40.1%
	17.6%	19.9%	15.5%		41.9%		
	av. 18.4%	av. 23.4%	av. 16.8%		av. 46.1%		av. 40.7%
30 min	13.9%	41.9%	43.1%	48.1%	59.8%	59.3%	64.5%
	16.2%	53.3%	39.7%	47.3%	57.6%	62.7%	74.9%
	57.6%	61.3%	44.2%	46.1%	60.9%	51.6%	77.1%
	39.1%	42.7%	41.6%	47.5%		51.2%	72.4%
	42.8%	15.0%	55.3%	49.8%		55.9%	71.2%
	53.1%	59.9%	12.5%	18.6%		52.8%	77.0%
	av. 47.2%	av. 50.7%	av. 44.4%	av. 47.9%	av. 59.6%	av. 55.6%	av. 72.8%
45 min.	53.1%	52.3%	47.5%		68.7%		
	63.9%	65.9%	50.1%		67.0%		
	60.3%	61.4%	47.8%		63.0%		
	av. 59.1%	av. 59.8%	av. 48.5%		66.5%		
					av. 66.3%		
60 min.	68.2%	59.4%	54.8%		74.8%		
	53.5%	65.2%	73.4%		71.7%		
	69.4%	73.3%	67.6%		69.4%		
	av. 63.1%	av. 65.9%	av. 65.2%		av. 71.9%		
75 min.	74.1%	76.0%	74.8%		80.0%		
	79.9%	73.8%	69.7%		81.2%		
	76.3%	78.7%	75.4%		81.4%		
	av. 76.9%	av. 76.1%	av. 73.3%		av. 80.9%		

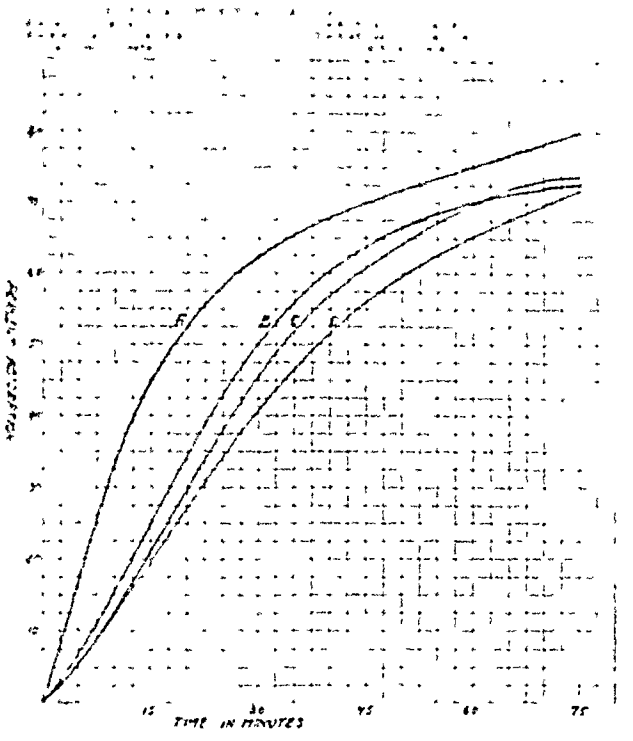


Fig. 1

covered in the urine which was collected for 48 hours (Table II).

Differences in the pH of the solutions introduced into the stomach affected the rate of absorption (Table III). Table III shows that solutions of acetylsalicylic acid and a mixture of acetylsalicylic acid and calcium gluconate which have pH's of 2.9 and 3.5 respectively are absorbed at almost the same rate (48.7% and 48.3%) whereas the solution of a mixture of acetylsalicylic acid and sodium bicarbonate (pH 7.3) is absorbed at the rate of 27.7% in one hour while only 19.0% of a mixture of acetylsalicylic acid and magnesium oxide (pH 9.09) is absorbed in the same time. When the pH of the acetylsalicylic acid solution was lowered from 2.9 to 1.7 by the addition of HCl, the absorption rate was increased from 48.9% to 58.1% per hour. At a pH of 1.25, 57.1% of acetylsalicylic acid was absorbed.

Experiments show no difference in the rates of hydrolysis of acetylsalicylic acid at these different pH's (Table IV).

No difference was found in the rate of diffusion of these various solutes through collodion sacs (Table V).

The urine gave a positive ferric-chloride test for salicylates in 10-15 minutes after the acetylsalicylic acid preparations were put into the stomach. Acetylsalicylic acid and sodium bicarbonate gave a positive test in 2 minutes while mixtures of acetylsalicylic acid and calcium gluconate or magnesium oxide gave positive tests in 15-35 minutes.

[illegible] The result of the rate of [illegible] the various [illegible] compounds [illegible] Table VI. [illegible] [illegible] 72% [illegible] acetylsalicylic acid and calcium gluconate (50.7%), acetylsalicylic acid and magnesium oxide (47.9%), acetylsalicylic acid (47.2%), and acetylsalicylic acid and sodium bicarbonate (44.4%). Curves obtained from the percentage absorption at fifteen minute intervals are presented in Figure 1.

DISCUSSION

Gastric Absorption: Quantitative recovery of only 50% of the acetylsalicylic acid introduced into the occluded stomach one hour previously, with a positive ferric-chloride test for salicylates upon the urine in 10-15 minutes leaves no doubt concerning the absorption of salicylates by the stomach. This was confirmed by perfusion of the pouch of the entire stomach in unanesthetized dogs. At the end of one hour the perfusate contained only 32% of the salicylate introduced; 68% had been absorbed. Of the amount absorbed 66% was recovered in the urine collected for 48 hours after the perfusion.

The rate of gastric absorption of these salicyl compounds appears to be dependent upon the size of the molecule and upon the pH of the solution. At similar pH's, salicyl compounds of small molecular size are absorbed at a faster rate (salicylic acid M. W. 138, 63.9% abs.) than compounds of a larger molecular weight (acetylsalicylic acid, M. W. 180, 48.9% abs.). This is demonstrated by the following equation in which molecular size and the average of the experimental data on absorption is introduced: 138:180:63.9:48.9. This is not true of the intestine.

There appears to be an optimum pH for the gastric absorption of these compounds. Greater absorption was obtained with acid pH's than with alkaline pH's (acetylsalicylic acid pH 2.9, 48.9% abs.), (acetylsalicylic acid and sodium bicarbonate pH 7.3, 27.7% abs.), (acetylsalicylic acid and magnesium oxide pH 9.09, 19.0% abs.), (acetylsalicylic acid and HCl pH 1.76, 58.1% abs.).

The rate of hydrolysis of acetylsalicylic acid has been found to be negligible at these pH's. Hydrolysis therefore does not play any part in the varying rate of absorption observed. Similar diffusion rates through collodion sacs indicate that this physical phenomenon cannot be responsible. Gastric absorption of these compounds therefore appears to be an active physiological process which is most rapid at acid pH's and which is related to molecular size.

Intestinal Absorption: Intestinal absorption of acetylsalicylic acid was not materially affected by the addition of "protective" compounds like calcium gluconate, sodium bicarbonate, and magnesium oxide. Absorption from the intestine was not so distinctly affected by the pH of the salicyl solutions, since the acetylsalicylic acid and its different mixtures were absorbed at almost the same rate. Compounds of a smaller molecular size (sodium salicylate, salicylic acid, and calcium salicylate) were absorbed at a faster rate than acetylsalicylic acid.

CONCLUSIONS

1. Salicyl compounds are readily absorbed from the stomach.

2. Gastric absorption is more rapid with the smaller salicyl molecule and at lower pH's.

3. Calcium gluconate, which does not materially [illegible] the pH of the acetylsalicylic acid solution, does not appear to affect the rate of gastric absorption.

4. Sodium bicarbonate and magnesium oxide which raise the pH of the solution inhibit the rate of gastric absorption of acetylsalicylic acid.

5. The rate of intestinal absorption of salicyl compounds is less affected by the pH of the solution than is their rate of gastric absorption.

6. Substances used to protect against gastro-intestinal irritation, such as calcium gluconate, sodium bicarbonate, and magnesium oxide, do not markedly influence the rate of intestinal absorption of acetylsalicylic acid.

7. Sodium salicylate, calcium salicylate and salicylic acid are absorbed from the intestine at a faster rate than is acetylsalicylic acid.

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The Control of Gastric Acidity in Peptic Ulcer by Alkalinized Powdered Whole Milk Tablets*

By

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BLAND foods and alkalies have been used in the therapy of peptic ulcer since early in the 19th century (1, 2, 5). Sippy (14) stressed the complete neutralization of gastric acidity, and in the past 20 years the value of this regimen has been demonstrated beyond doubt (6, 13). The administration of alkalies seems, at present, to be the most direct way of neutralizing the gastric secretion, and when this procedure fails it is because the patient has not followed the minute instructions necessary. Furthermore, physicians often fail to check the effect of the prescribed alkaline powders and foods on the acidity. Recent experimental studies have pointed to the long suspected importance of acid in the production and continuation of chronic ulcers (8, 9, 10, 11, 12). Therefore, in this report the neutralization of gastric acidity in the treatment of peptic ulcer is considered not only desirable but fundamental.

While cow's milk has been the mainstay of the usual bland diet prescribed for peptic ulcer, it is not considered "the perfect food" by many authors who have found it unsafe from the bacterial standpoint (15), a frequent cause of distress (3), and productive of a tough, hard curd capable of producing spasm of the pylorus (4). However, certain modifications of sweet cow's milk minimize these objections, and it occurred to Wosika and Emery (16, 17) that a mixture of powdered whole milk combined with alkali powders in the form of tablets might be superior to the usual Sippy regimen.

A previous paper (16) evaluated the effect of the routine Sippy treatment on the control of acidity on 46 patients with duodenal ulcer. It was found that symptoms were abolished and that the free acidity was adequately controlled in slightly more than one-half of the patients. A second report (17) compared the use of a liquid mixture of powdered whole milk plus an alkali powder, with the routine Sippy procedure, and demonstrated that the former was the more effective as a neutralizing agent.

The purpose of the present study is to determine the value of tablets composed of powdered whole milk and varying amounts of alkalies on the neutralization of the gastric acidity in patients with peptic ulcer. If the use of these tablets proves as efficacious as the usual Sippy procedure, then this convenient means of neutralizing the stomach contents should prove to be a remedy worthy of inclusion in the physician's armamentarium for this disease.

METHOD AND DATA

For this study 26 cases of peptic ulcer were selected from the Medical Clinic of Northwestern University. Roentgenological evidence for ulcer was positive in all save 2 cases and the clinical history of both of these exceptions was too typical to doubt. All of the patients were men between the ages of 26 and 66 years. The average age was 44 years. Ulcer symptoms had been present from 1 to 20 years, with an average of 9 years. Three of the group had gastric ulcers, and because they had relatively high acid values as determined by a histamine gastric analysis, they were included in the series. All the men were in poor financial circumstances; the two patients who were not on relief were unemployed.

The patients reported to the clinic about once weekly in the morning, and all meals (the usual foods allowed on the fourth week Sippy regimen) were served at Passavant Memorial Hospital at 8:00 a.m., 1:00 p.m., and 6:00 p.m. Between meals they were given tablets or milk and cream as will be indicated. From 8:00 a.m. until 7:00 p.m. 6.0 c.c. specimens were aspirated every half hour and were titrated in the customary manner for free and total acid. The pH values were determined with the quinhydrone electrode. The

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various readings were averaged and the results may be seen in the following figures.

Figure 1 shows the average free and total acid (solid lines) and pH (broken line) on 23 patients who were given the fourth week regimen. Between meals they received 90 c.c. of milk and cream on the hour and on the half hour an alkaline powder (2.0 gm. sodium bicarbonate and 0.6 gm. calcium carbonate). The free acid curve may be seen to increase steadily in spite of the regular and frequent feedings until an average reading of 25 clinical units occurs. A precipitous drop

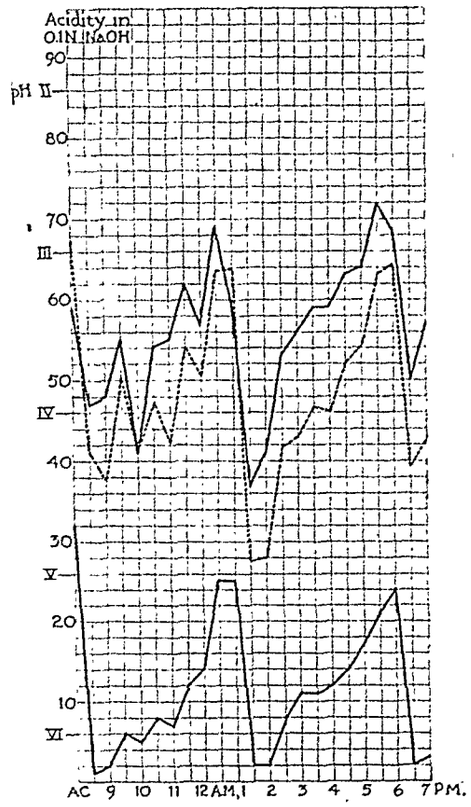


Fig. 1. Average free and total acid (solid lines) and pH (broken line) on 23 patients receiving 90 c.c. milk and cream on the hour, and 2.0 gm. sod. bicarb. and 0.6 gm. calc. carb. on the half hour.

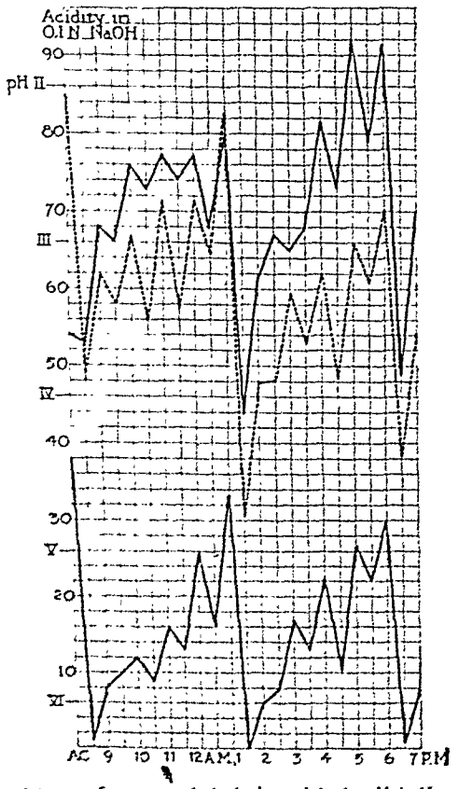


Fig. 2. Average free and total acid (solid lines) and pH (broken line) on 22 patients receiving 90 c.c. milk and cream plus a routine Sippy powder. Half hour feedings omitted.

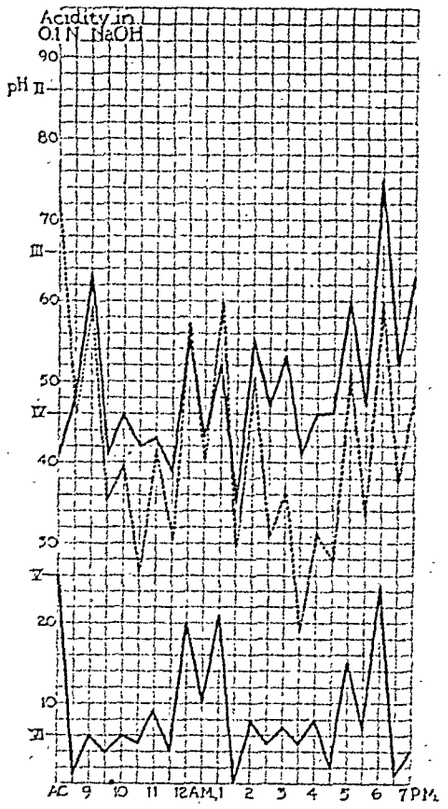


Fig. 3. Average free and total acid (solid lines) and pH (broken line) on 28 patients receiving 12.5 gm. powdered whole milk, 2.0 gm. sod. bicarb. and 0.6 gm. calc. carb. on the hour in four tablets (7115-O and O1) and nothing on the half hour.

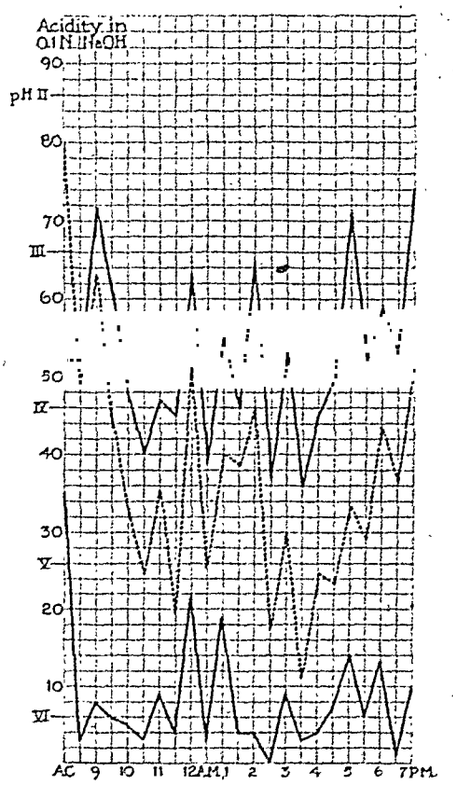


Fig. 4. Average free and total acid (solid lines) and pH (broken line) on 20 patients receiving 15.6 gm. powdered whole milk, 2.5 gm. sod. bicarb. and 0.75 gm. calc. carb. on the hour in five tablets (7115-O and O1) and nothing on the half hour.

follows dinner and similar declines may be seen after breakfast and supper. The total acid curve follows the free acid closely. The pH range for the entire day is between 3 and 5. This chart shows clearly that for these 23 male patients, the Sippy procedure, as used routinely, is inadequate for the complete neutralization of the free acid. It may also be inferred that one or two aspirations daily as is customary is insufficient for gaining an accurate picture of the acid present.

Appreciating that a smaller curd in the stomach might reduce the amount of acid, the routine powder was mixed with the milk and cream and given every

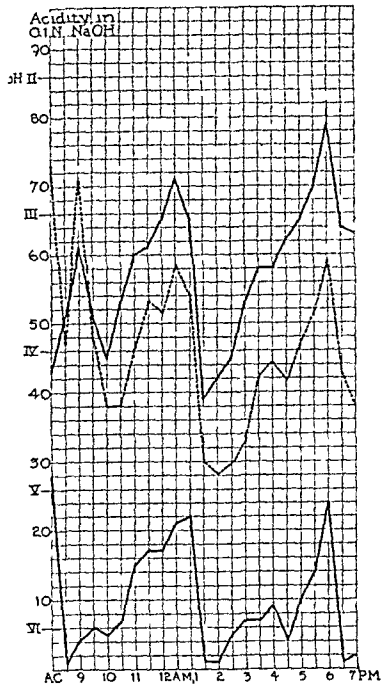


Fig. 5. Average free and total acid (solid lines) and pH (broken line) on 21 patients receiving 6.25 gm. powdered whole milk, 1.0 gm. sod. bicarb. and 0.3 gm. calc. carb. every half hour in two tablets (7115-O and O1).

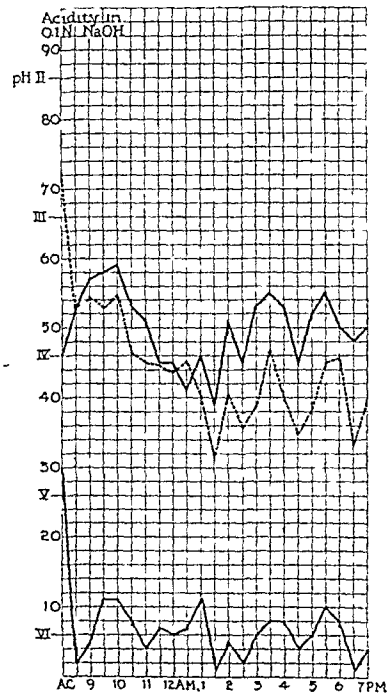


Fig. 6. Average free and total acid (solid lines) and pH (broken line) on 19 patients receiving 6.25 gm. powdered whole milk, 0.3 gm. sod. bicarb. and 1.0 gm. calc. carb. every half hour in two tablets (7115-Q or T).

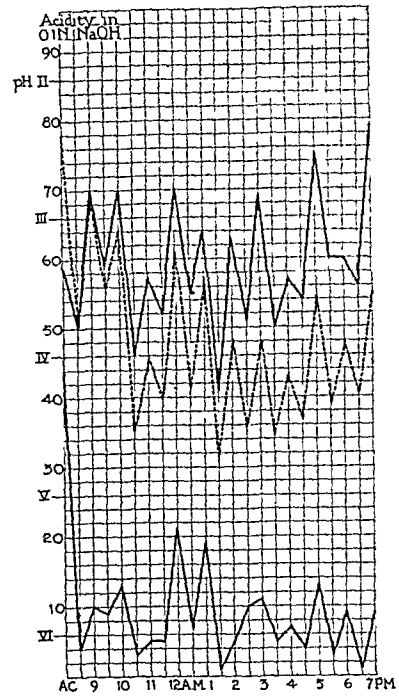


Fig. 7. Average free and total acid (solid lines) and pH (broken line) on 21 patients receiving 12.5 gm. powdered whole milk and 1.0 gm. each sod. bicarb. and calc. carb. in four tablets (7115-R or S) and nothing on the half hour.

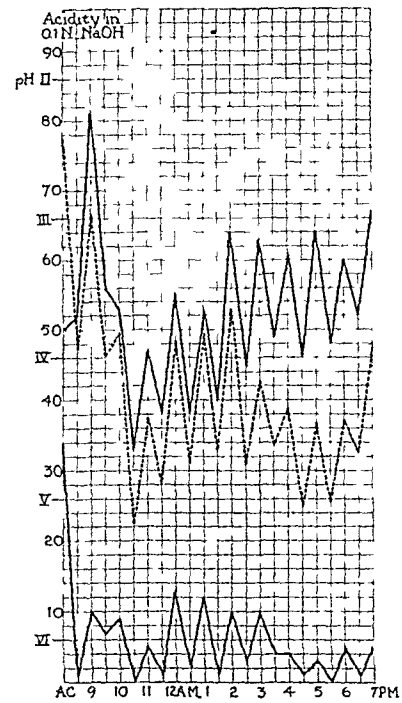


Fig. 8. Average free and total acid (solid lines) and pH (broken line) on 19 patients receiving 15.6 gm. powdered whole milk and 1.25 gm. each of sod. bicarb. and calc. carb. on the hour in five tablets (7115-R or S) and nothing on the half hour.

hour. The half hour feedings were omitted. Figure 2 depicts the average free and total acid (solid lines) and pH (broken line) on 22 patients when these hourly feedings were dispensed between the three meals. The free acid in this instance could not be considered controlled at any time except immediately following the meals. The total acid range is higher with this alkalinized powdered whole milk (Figure 2) than on the fourth week Sippy diet (Figure 1). This apparent stimulation of acid secretion is also reflected in the

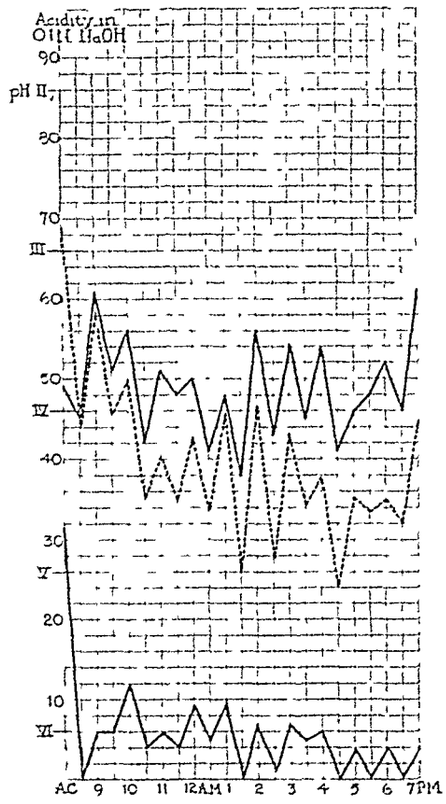


Fig. 9. Average free and total acid (solid lines) and pH (broken line) on 24 patients receiving 12.5 gm. powdered whole milk, 0.6 gm. sod. bicarb. and 2.0 gm. calc. carb. on the hour in four tablets (7115-Q or T) and nothing on the half hour.

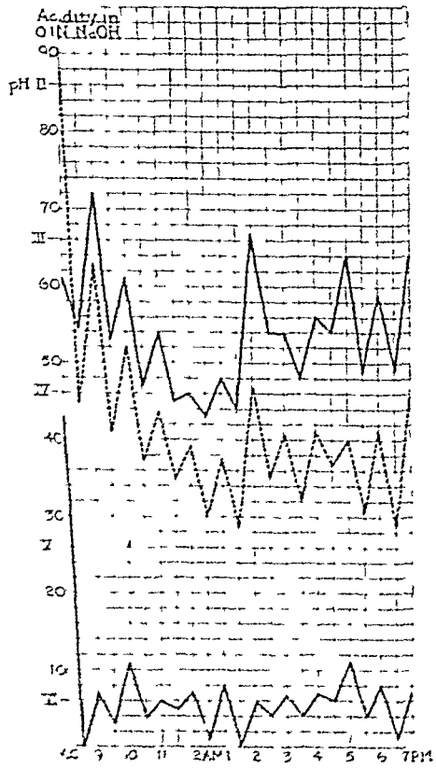


Fig. 10. Average free and total acid (solid lines) and pH (broken line) on 23 patients receiving 15.6 gm. powdered whole milk, 0.75 gm. sod. bicarb. and 2.5 calc. carb. on the hour in five tablets (7115-Q or T) and nothing on the half hour.

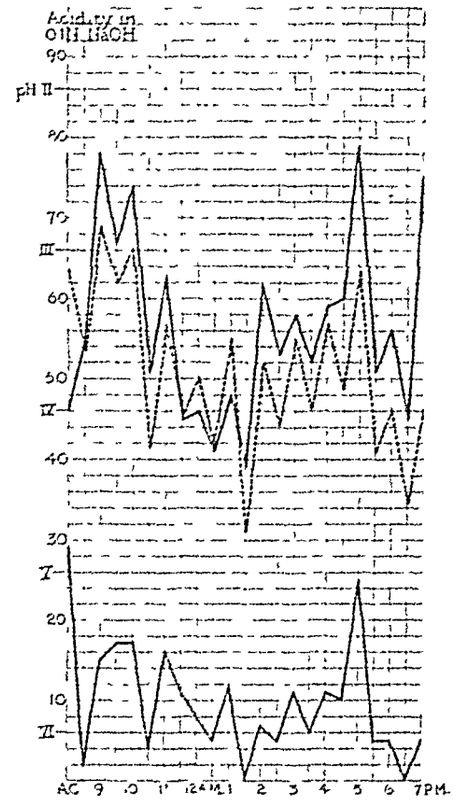


Fig. 11. Average free and total acid (solid lines) and pH (broken line) on 16 patients receiving 12.5 gm. powdered whole milk and 2.4 gm. calc. carb. on the hour in four tablets (7115-B3) and nothing on the half hour)

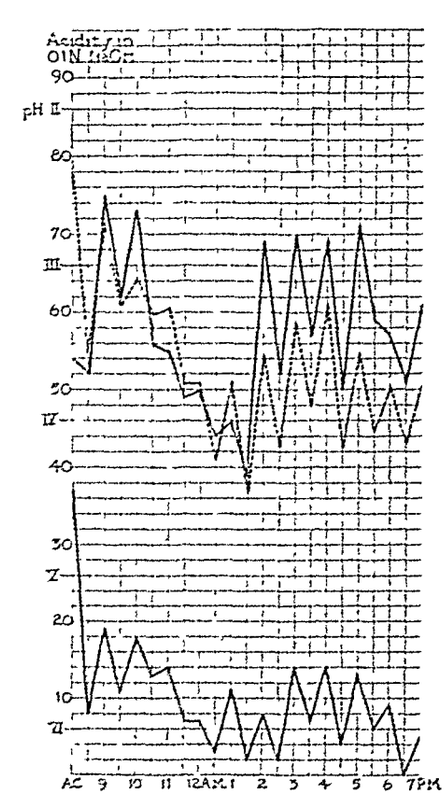


Fig. 12. Average free and total acid (solid lines) and pH (broken line) on 16 patients receiving 15.6 gm. powdered whole milk and 3.0 gm. calc. carb. on the hour in five tablets (7115-B3) and nothing on the half hour.

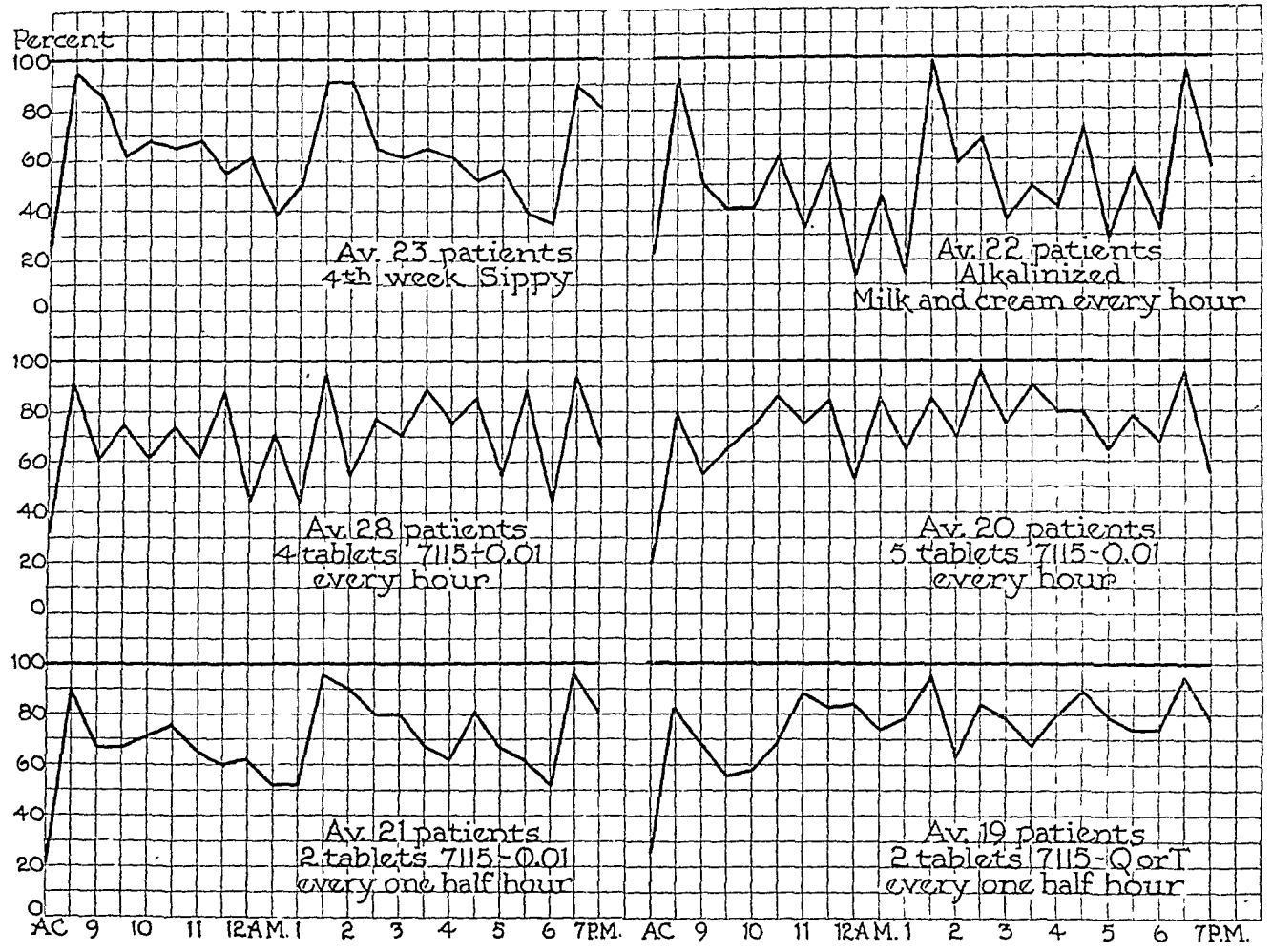


Fig. 13. Percentage of patients who revealed no free acid at each half hour analysis throughout the day.

lower pH curve. It should be remembered that exactly the same amount of food, milk and cream, and powders were used for these tests, the only difference being that the powder was mixed with the milk and the half hour feedings were omitted. If these average free and total acid values, as given on Figures 1 and 2, are averaged for the entire day, then 56 clinical units represent the total acid for the Sippy and 71 units the alkalinized milk and cream. This means that for 21 specimens collected at half hour intervals for the entire day the total acid is stimulated 15 clinical units on the latter procedure. These figures may be seen in Table I.

TABLE I

Average values of the 21 free, total and pH readings. Each line on Figures 1 to 12 is represented by one number

Procedure	pH.	F.A.	T.A.
Fourth Week Sippy	3.93	11	56
Alkalinized Milk and Cream	3.40	14	71
7115-O or O1—4 every 1 hour	4.28	8	49
7115-O or O1—5 every 1 hour	4.55	7	53
7115-O or O1—2 every ½ hour	4.09	9	58
7115-Q or T—2 every ½ hour	4.14	6	50
7115-R or S—4 every 1 hour	3.91	8	59
7115-R or S—5 every 1 hour	4.36	5	53
7115-Q or T—4 every 1 hour	4.37	5	49
7115-Q or T—5 every 1 hour	4.32	5	54
7115-B3—4 every 1 hour	3.71	9	57
7115-B3—5 every 1 hour	3.68	9	58
Histamine Gastric Analysis	1.44	61	84

Figure 3 shows the average free and total acid curves of 28 patients who were given three meals, but the interval feedings were 4 tablets (7115-0 or 01), containing 12.5 gm. powdered milk, 2.0 gm. sodium bicarbonate, and 0.6 gm. calcium carbonate given every hour. Nothing was given on the half hour and only 90 c.c. of water was allowed with the tablets, equalizing the factor of dilution. The free acid curve did not rise consistently to peaks before meals. The peaks were present but were delayed in their development for 3½ hours during which time the average reading was under 10 clinical units. The inference seems logical that the simple omission of the half hour feedings is not the cause of the rise in acid values that was noted on Figure 2. Also, the total acid values were lower than on either test with milk and cream. The average total acid measurement for the day is 49. The pH readings in general follow the other curves and

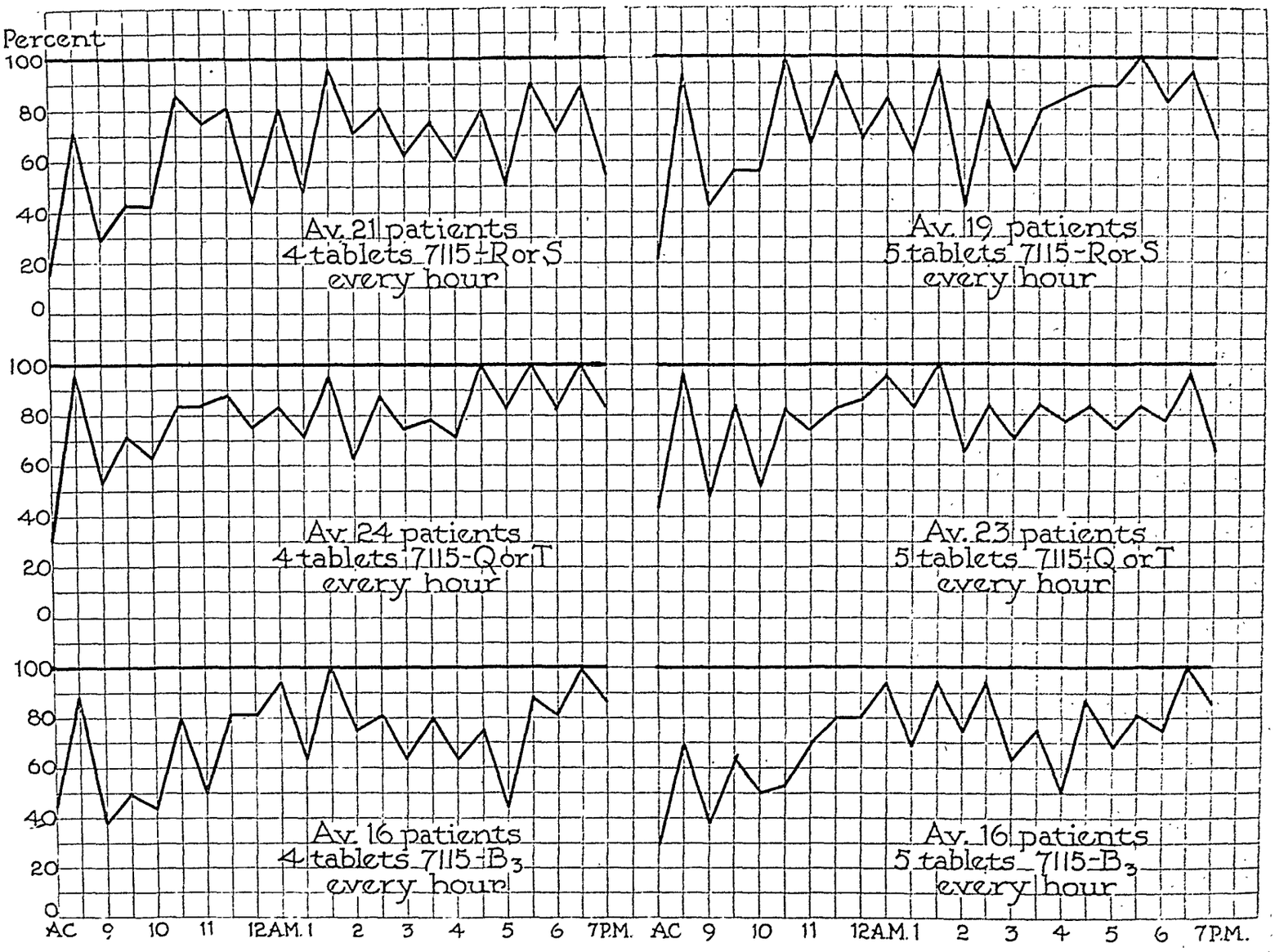


Fig. 14. Percentage of patients who revealed no free acid at each half hour analysis throughout the day.

show that lower amounts of acid were present than when milk and cream were used.

These results were not as satisfactory as had been obtained with exactly the same materials in a fluid form (17). The compressing process necessary in the manufacture of the tablets was thought to be responsible for the lowered effectiveness. Disintegration would not be so complete, making neutralization more difficult. To overcome this suspected complication, one-quarter more material was given. Thus, 5 tablets (7115-0 or 01) were administered every hour and the average results on 20 patients may be seen on Figure 4. The other factors remained the same. In this test the patients received on the hour 15.6 gm. powdered whole milk, 2.5 gm. of sodium bicarbonate, and 0.75 gm. of calcium carbonate. It becomes apparent from inspection of the chart that the mere increase in quantity will not overcome the high acid values noted. While the pH curve is lower for the day on the procedure, the results do not justify the increased amount of alkali administered.

Figure 5 shows the average free and total acid (solid lines) and pH (broken line) on 21 patients who were given 2 tablets on the hour and 2 tablets on the half hour (7115-0 or 01). The lack of acid control here is obvious. The curves suggest that the half hour feeding might be stimulating to acid secretion.

Four of the high calcium tablets (7115-Q or T) contain 12.5 gm. powdered whole milk, 0.6 gm. sodium bicarbonate, and 2.0 gm. calcium carbonate. Two of these tablets were given to 19 patients every half hour and the average free and total acid and pH is shown on Figure 6 by the usual lines. The curves do not show the wide variations noted on the previous charts. This would tend to minimize the importance of the half hour feedings in the stimulation of acid if and when the amount of sodium bicarbonate is decreased.

Another type of tablet tested contained per "dose" of 4 tablets 12.5 gm. of powdered whole milk and 1.0 gm. each of sodium bicarbonate and calcium carbonate. Figure 7 reveals the average effect of 4 of these tablets once an hour (7115-R or S) on the gastric acidity on 21 patients. This represents a reduced amount of soda from the routine tablets. The free acid curve (solid line) does not show the steadily mounting values that are apparent when tablets with larger amounts of soda are used. In general, the free acid is lower than on either of the tests when milk and cream were employed. The average values are slightly higher than when other tablets are considered (Table I). The gastric acidities of 19 patients were again studied when 5 such tablets (7115-R or S) were given every

hour. These 5 tablets contained 15.6 gm. powdered whole milk, and 1.25 gm. each of calcium carbonate and sodium bicarbonate. The average results are shown in Figure 8. The free acid averaged over 10 clinical units only on two occasions. Table I shows the average free acid to be as low as with any other material assayed. The pH and total acid compared very favorably with those noted on Figures 2 and 3.

Because the reduced amount of sodium in the tablets (7115-R or S) seemed to be an improvement to those of the routine type (7115-0 or 01), the quantity of sodium was reduced still further. This resulted in the high calcium tablets (7115-Q or T). Four of these tablets contain: 12.5 gm. powdered whole milk, 2.0 gm. calcium carbonate, and 0.6 gm. sodium bicarbonate. Figure 9 exhibits the average effect on the gastric acidity of 24 patients who were given 4 of these tablets on the hour. The free and total acid are represented by solid lines and the pH by the broken line. Wide variations of acid values are not manifested with these tablets. The free acid reading is low for the entire day and the average for the 21 analyses was 5 clinical units. The total acid was lower on the average than was found with any other procedure. The pH was higher than on tests using tablets with a larger amount of sodium bicarbonate. Twenty-three patients were studied similarly using 5 tablets (7115-Q or T); the additional tablet increasing the ingredients to 15.6 gm. powdered whole milk, 2.5 gm. calcium carbonate, and 0.75 gm. sodium bicarbonate. The average results seen on Figure 10 do not justify the increase in powdered milk and alkalies. The pH is slightly higher, the free acid averages the same, and the total acid is elevated above that reached by the 4 tablets.

The next obvious step was to attempt to control the gastric acidity with tablets made without any sodium bicarbonate. Four of these (7115-B3) were composed of 12.5 gm. powdered whole milk, and 2.4 gm. calcium carbonate, and when administered every hour, the average effectiveness on the acidity on 16 patients is shown in Figure 11. Figure 12 depicts the efficiency of 5 of these tablets (7115-B5) containing 15.6 gm. powdered whole milk, and 3.0 gm. calcium carbonate given on the hour to the same 16 patients. These tablets were inadequate for neutralizing the gastric acidity. The free acid was higher in both instances and the pH lower than when soda was used. Thus, even though sodium bicarbonate seems to stimulate acid secretion, when soda was removed from the tablets, their efficacy, as judged by the free acid control, was decreased.

Figures 13 and 14 show the percentage of patients whose acidity was absolutely zero at each half hour period throughout the day. Again, the high calcium tablets (7115-Q or T) are seen to produce a negative free acid reading in the highest number of patients in this series. This is true if 4 or 5 of these tablets are dispensed or if 2 are administered every half hour.

Table I shows the values obtained when each line on the charts were reduced to one figure. The 21 free, total acid, and pH readings have been averaged and all show a remarkable similarity. The free acid averages between 5 and 14 units. The total acid varies between 49 and 71 clinical units, while the pH varies between 3.40 and 4.55.

COMMENT

It might be well to re-emphasize the type of patient used in this series of analyses. All of the patients were male and worried about their poor financial condition. They had poor teeth or none, and adequate care for the obvious gingivitis was not possible. Certainly the conditions were not ideal for the treatment of ulcer patients when the usual admonitions are considered: Rest, freedom from worry, and elimination of foci of infections.

Ambulatory treatment was the rule and symptoms were easily controlled. Tablets were supplied for the intervals between tests at the laboratory and presumably were consumed. At best, however, treatment must be considered to have been rather haphazard when the patients were away from the clinic.

Alkalosis was not a problem. Whenever the slightest suspicion of this would arise clinically the carbon dioxide combining power of the blood was determined. No unusual values were found. Persistent headaches in one patient were relieved by the removal of several nasal polypi.

Considering the series of patients, the results were not so satisfactory as was reported earlier using a liquid mixture. However, instead of the hospitalization that had been used before, these patients were tested in a large laboratory room where many other experiments (chiefly animal) were in progress, with all their attendant odors. Therefore, while it is impossible to compare the earlier results obtained with these, the tablets of powdered whole milk are seen to be superior to the milk and cream feedings of the Sippy regimen for the neutralization of the gastric acidity.

One reason for the lower acid values when the powdered whole milk was used was because of the smaller curd produced with this material in the stomach. Observations on the curds were collected on specimens, using the Hill Curd-o-meter (7) and average values follow:

Material	Curd Tension in Grams
Milk and cream	43.0
Alkalinized milk and cream	10.4
Powdered whole milk	13.0
Alkalinized powdered whole milk	3.5
Tablets (crushed, 7115-O, routine)	5.6
Tablets (crushed, 7115-Q, high calcium)	5.4

These materials were the same in every respect with what had been administered to patients.

It is obvious from these figures that the reduced curd tension is so marked with the powdered whole milk that the beneficial effect of its use in diseased stomachs merits further consideration.

No attempt is being made to formulate a "new mode of therapy" for peptic ulcer. In this study Sippy's observations, as well as those made in the previous century on alkali therapy, are accepted as fundamental. These tablets may best be used if and when they are found to neutralize the gastric contents of the individual patient. The high calcium tablets (7115-Q or T) seem superior from the standpoint of effectiveness on the gastric acidity and taste, which latter improved markedly when the amount of soda was decreased. The

tablets are convenient and pleasant enough to take without water if necessary. Four of these may be safely recommended to patients to be taken every hour, thereby reducing by one-half the usual feedings of the routine Sippy regimen.

SUMMARY

It has been found by a study of 26 male patients with peptic ulcer that tablets composed of powdered whole milk (12.5 gm.), sodium bicarbonate (0.6 gm.), and calcium carbonate (2.0 gm.) are slightly more effective than the routine Sippy procedure as regards the neutralization of the gastric acidity.

Miss Florence Burdahl gave expert technical assistance.

The author wishes to express his appreciation for the helpful criticisms and suggestions of Drs. Charles A. Elliott, Clifford J. Barborka and Lathan A. Crandall in the preparation of this manuscript.

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Annual Abstracts of Proctologic Literature

(May, 1934-May, 1935) By CLEMENT L. MARTIN, M.D., Chicago, Illinois

The complete bibliography from which these Abstracts were made will be published in full in the Transactions of the American Proctologic Society, 1935.

PRURITUS ANI

Hermance and Bacon in their contribution to Piersol's Cyclopedia of Medicine give a very concise description of the condition, the actual causes are briefly enumerated and accepted treatments given. Evaluating the treatments as they so well could have done would have helped the general practitioner but might have caused rejection of their copy in a cyclopedia.

Terrill writes as one who has cared for many cases of the disorder, he reviews the various theories and treatments and regards allergy as a factor in few cases and states "My opinion is that fully 90% of the cases that came to me are primarily of fungal origin, although many of them become secondarily infected with other organisms." He advocates constant hot dressings of mercuric bichloride 1-5000 in the acute stage and the substitution of a milder solution or a powder if drug dermatitis develops; in the subacute or chronic state, an alcoholic solution of red iodide of mercury. The incidence of trichophyton infections of the perianal skin is much less than 90% in the middle West in the Reuiewer's opinion.

The Philadelphia post-graduate group report on Gabriel's A.B.A. solution, nupercaine in oil, sterile distilled water, autogenous vaccine, and undercutting operations. We are fortunate to have such reports available. A cure has not been found. The "Resume of Experimental Studies . . . ." by Bacon should be read in full.

PHYSIOLOGY

The study of the innervation of the colon, especially the distal portion has been stimulated by the operation sympathectomy. Intradural alcohol injections are limiting and may largely replace this operation for the relief of intractable pain in the patient with inoperable pelvic cancer.

Several informative papers have appeared on colonic function. The question of glucose absorption has stimulated several investigations. *Bargen* and his associates, using the distal colonic segments in colostomized patients in their investigations, conclude that these distal segments were shown to absorb methylene blue which subsequently was excreted in the urine; atropine which caused pupillary dilatation and decreased salivation; sucrose which subsequently was excreted in the urine and in the stools from the proximal colonic segment; and glucose, which disappeared from the colonic segment, accompanied by an increased respiratory quotient or increased heat production or both. In the presence of impaired utilization of carbohydrate, increases in values for peripheral blood sugar accompanied this process.

Distal segments of the colon of man did not excrete: methylene blue, which had been orally administered in amounts sufficient to appear in the urine; glucose when 25 grams of it had been intravenously administered; sucrose, when 5 grams of it had been intravenously administered. Arsenic, when administered orally as treparsal was excreted by distal colonic segments in amounts which in some instances exceeded the urinary excretion over the same period of time.

Cutting determined by experiments in dogs that "the colon and ileum absorb dextrose from 5 and 10% solutions but they absorb less from a 10% than from a 5% solution."

Ebeling studied the absorption of dextrose solutions from colon loops in dogs and found the method satisfactory. He concludes that absorption of glucose from the colon is not adequate for clinical needs. He concludes that

hypertonic solutions (over 5%) may be harmful due to extraction of water from the tissues.

A report on *Schnohr's* "Study on the cause of death in high intestinal obstruction" reveals a study based on body fluids and body chlorides. Giving hypertonic solution of sodium chlorides prolongs life by increasing elimination of toxins by increased urine flow.

White, Rainey, et al, made observations on a patient whose cecum and terminal ileum had prolapsed through an old cecostomy wound and found among other facts that in this case the ileo-cecal sphincter was relaxed much of the time, definite antiperistalsis was not seen in the proximal colon, inhibition waves did not precede contraction waves, rythmic contractions persisted during the passage of peristaltic waves, pituitrin consistently gave some increase in the activity of the colon and diminution in tone or rythmic activity of the ileum, the ileocecal sphincter was consistently relaxed by adrenalin.

Buie and Brust have published an excellent study of 100 cases having high rectal pain. The cause of pain was not found in 19, in 26 chronic nervous exhaustion appeared to be the logical diagnosis, 12 were regarded as psychoneuroses, rectal neuralgia was diagnosed in 12, 8 had tabetic crises, 5 radium proctitis, 6 prostatic disease. Pelvic tumor, sacrococcygeal arthritis, adenomyoma of the recto-vaginal septum accounted for most of the remainder. There was one case of each of the following: neurosis, rectal neurosis, coccygodynia, cystocele and rectocele, chronic pelvic inflammatory disease. Further synopsis is impractical, the article should be read.

STRICTURE

Many of the current articles on the subject deal chiefly with lymphogranuloma inguinale.

Bacon, et al, report 24 cases of stricture of the rectum treated by Jelk's operation. They believe the operation is especially indicated in stricture due to extra-rectal infection. Postoperative dilatation for a long time is essential to maintain the size of the lumen.

Collins and Jones report a series of 422 cases of cervical carcinoma in which irradiation therapy was administered; 6 patients presented the late complication of a benign stricture of the rectum (incidence 1.4 per cent). Of the 6 cases reported 5 of the benign strictures occurred in the sigmoid colon and 1 in a lower loop of the small intestine. Because of the unusual fixation of the involved area, sigmoidoscopic examination may not reach the lesion in patients having a sigmoid lesion. Colon roentgen examination was the most important single preoperative diagnostic means of revealing stricture of the sigmoid. This rare complication was successfully treated by surgical intervention and they feel that it should not constitute a retarding influence on irradiation therapy.

SYMPTOMATOLOGY

In *Blond's* article is a viewpoint of interest, namely, that there are many cases of "nodules of the anus, fissures, and pruritus in which hyperemia or varices, either under the skin or mucosa, is not present."

SYMPATHECTOMY

See Physiology

Davis found the "presacral nerve" to be usually a plexus. He believes the main effects are on a vasomoter basis although the plexus probably has motor, glandulo-motor, and nutritional functions. He reports about 50% cures.

Behney reports 22 operations for resection of the pelvic antonomic nervous structures for pelvic pain with complete relief in 72%. Diarrhea and urinary incontinence were common the first week following operation.

Atlee reports a favorable percentage with respect to cure and partial relief of pelvic pain following pre-sacral sympathectomy.

THERAPEUTICS

Swalm states the compound of aluminum silicate (kaolin) with aluminum hydroxide in certain intestinal disorders has been shown both experimentally and chemically to possess greater efficiency than kaolin alone.

MacNeal, et al, believe that a specific bacteriologic diagnosis should generally precede the therapeutic use of bacteriophages. The preparation of bacteriophages, active against the colon bacillus, presents particular problems. The use of bacteriophage for colonic disease has not attained wide acceptance.

Warren is investigating the effects of artificial fever on hopeless tumor cases and although he has obtained no results approaching cure he obtained some encouraging effects. Combined fever therapy and deep therapy may show better results.

TUBERCULOSIS

Light therapy, diet, rest and general hygienic measures continue to be the principal treatment of intestinal tuberculosis. Those who use light therapy extensively feel that it is a valuable adjunct in their hands.

Frederick C. Smith reports on ano-rectal tuberculosis and describes the tuberculous conditions which may occur in this area.

Boles and Gershon-Cohen analyzed 1000 consecutive autopsies at Philadelphia General Hospital to determine the incidence of intestinal tuberculosis with relation to pulmonary tuberculosis. Its highest incidence was in cases of fibroulcerative cavernous pulmonary tuberculosis, "one might suspect in this group that there is no intestinal ulceration without pulmonary ulceration." It was present in only 18% of early or exudative cases. It was not observed in any case of chronic fibroid or miliary tuberculosis. Primary hyperplastic tuberculosis or tuberculoma was not seen in their series. They conclude that "a strong inferential diagnosis of the disease can be made when one considers it in its relation to the various types of pulmonary tuberculosis and as a result of evidence secured by the double contrast barium enema."

It will be noted that *J. Westermann* reports an abdominal perineal resection for tuberculosis involving the sigmoid and rectum.

VENEREAL DISEASES OF THE RECTUM

(1) Gonorrhea

Cyril V. Black working with Dr. Tucker concludes in "Gonorrheal Infection in the Female" that re-infection from the rectum has occurred in women and that it may be relatively symptomless for a long time. He discusses the use of Theelin in aqueous solution and the Elliott method of treatment for the condition. 83% of the gonorrhea cases had rectal disease, 66% had rectal gonorrhea.

Bierman and Horowitz note that re-infection of the genital tract has occurred from the rectum.

This matter is given very little consideration, or if considered has been thought to be of little consequence by gynecologists generally.

(2) Syphilis

Buie and Butsch report a case of tertiary syphilis having multiple fissures of the anus. The patient was a woman aged 50. They note that constant discomfort in this case was a significant point in the history, unlike hemorrhoids or fissure in which discomfort is apt to be of an intermittent character.

PROLAPSE

The number of operations advised for the relief of the more severe cases of rectal prolapse attest to the fact that a uniformly satisfactory procedure for third degree prolapse has not been devised as yet. The Moschovitz operation, partially obliterating the pelvic cul-de-sac or the method of anchoring the sigmoid well up to the psoas

tendon give permanent results in selected cases. I have at times wondered how a general surgeon without great experience in this particular field would solve his problem after investigating the literature; his state would probably be "confusion worse confounded."

That third degree prolapse is essentially a hernia is a well founded assumption. However, many of the operations devised on this basis, especially those which attempt to identify isolate and shorten anterior, posterior, or lateral "ligaments" of the rectum are working with inconstant or poorly defined fascial bundles. Most operations of this group are complicated procedures with uncertain results.

In the British Medical Journal of last year, several men discuss injection therapy as applied to prolapse: Morley favors it because there is no operative risk or loss of time. Findlay uses alcohol, inserting the needle through the skin just outside the anal canal rather than through the mucosa, and advances it up along each side of the rectal wall a distance of about 2½ inches. Williamson injects alcohol from the perineum and holds the rectum up toward the coccyx by a silk-worm-gut suture for about 10 days to keep it in position while adhesions are forming. Chesser uses ionization for hemorrhoids and prolapse. Smith repairs the perineum in males with prolapse, as a perinorrhapy is done in the female, to restore the normal angulation of the anus and its normal relation to the rectum. Cannon regards rectal prolapse as a type of sliding hernia and states that it requires repair of the perineal and lateral supporting structures. He believes that the lateral supports of the rectum are defective as well as the sphincters and levatores ani. He does not believe in the injection treatment. Carrasco has published a 196 page book in French on the subject.

HISTORY

Although the name of Bodenhamer crops up every now and then as one reads the literature of rectal disease, few of our generation have more than a vague notion of his character or accomplishments. *Kleiner's* sketch of his life indicates that he was forceful and aggressive but selfish and not over-burdened by a regard for medical ethics, that he was capable, a student, and that his publications helped to advance the study of proctology.

SECTION VIII—*Editorial*

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastro-enterological Association is in no way responsible for editorial expressions.

THE ALL-OR-NONE LAW AND THE PARIETAL CELLS OF THE STOMACH*

THE all-or-none law appears to have been first formulated by Bowditch, in 1871, in the following terms: "An induction shock produces a contraction or fails to do so according to its strength; if it does so at all it produces the greatest contraction that can be produced by any strength of stimulus in the condition of the muscle at that time." (Bayless, 1915). In view of the outstanding importance which this principle has assumed in the field of nerve-muscle physiology, it is not at all surprising that several attempts have been made to apply it to the glands of external secretion as well. In the case of the gastric secretions, the first suggestion on record in this direction was made by Kahn and Yaure (1924). With the acquisition of further evidence concerning the characteristics of the parietal secretion, Babkin (1931) adopted a similar view of the matter. "If the secretory cells are subject to the 'all or none law,' *i.e.*, that they produce either a maximum of secretion or none, then the greater effect of a stronger stimulus may be explained by the greater number of glanular cells involved in the secretory process. It seems probable that the parietal cells are subject to the 'all or none' law."

Neither of the above passages, however, attempts to analyze secretory action into the several component factors which underlie the all-or-none law as it is applied to nerve and muscle. The first effort in this direction was made by Liu, Yuan, and Lim (1934); in a discussion of some of their earlier work they say: ". . . the response of the oxyntic cells is 'all or none,' as they found that the HCl 'amplitude' or concentration is virtually constant and independent of the intensity of stimulation, while the HCl rate or output varies in relation to the stimulus. The conception of concentration as amplitude, and output as rate or frequency of function places secretory activity on the same physiological basis as contraction and conduction . . . . . Hollander and Cowgill (1931) have published results which support the above view." The interpretation placed upon the work of Cowgill and myself in this quotation is not in accord with my views on the subject, although the results have definitely established the fact that the millimolar concentration of HCl in the parietal secretion is constant and of such magnitude as to be practically isotonic with the tissue fluids. (Hollander, 1934, a). On the contrary, and in spite of the characteristic nature of the secretion, I believe that at the present time there exists no evidence whatever for maintaining that the parietal cells obey the all-or-none law. A similar view regarding the inapplicability of the law to salivary secretion is developed by Barcroft (1934). Since the applicability of the law to the parietal cells is coming to be accepted more and more by gastric physiologists, it seems desirable to present an analysis of the situation which may help to clarify the issues involved.

Let us first specify the several factors which are pertinent to the problem. In the case of striated muscle these are: (1) the intensity of the applied stimulus, (2) the number of muscle fibers contained in the muscle bundle being studied, and (3) the maximal response (i.e., contraction) of each fiber which is possible under given environmental conditions, (e.g., osmotic pressure and pH of the surrounding tissue fluid). According to the all-or-none law, under a given stimulus an individual muscle fiber will respond either

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with this maximal contraction or not at all. A partial response of a single fiber is impossible. Therefore, the gradation in height of contraction of the entire muscle bundle, which may be observed with a variable stimulus, is due to a variation in the number of fibers which may have responded to the stimulus at any one time. A maximal contraction of an entire muscle implies a maximal functioning of all the fibers; a submaximal contraction implies a maximal functioning of only some of the fibers. This is all quite elementary—for striated muscle.

In the case of the parietal cells, however, there are four factors instead of three; namely, (1′) the intensity of stimulus which is applied to the secreting organ, and which might be measured by the amount of histamine which reaches that organ in unit time, (2′) the number of individual parietal cells, not glands, contained in the organ, (3′) the volume of parietal secretion poured out by each cell in response to the stimulus, and (4′) the composition of this acid secretion. Since this fluid contains practically nothing other than hydrochloric acid and water (Hollander, 1934, b) this last factor, the composition, may be expressed simply as the concentration of HCl in the parietal fluid. Although we are as yet unable to measure (1′) and (2′) precisely, nevertheless these two factors are entirely analogous to the corresponding ones for muscle contraction. It is in relation to (3′) and (4′) that the difficulty arises. The degree of activity of a single muscle fiber is measured by its height of contraction, (3), whereas for the parietal cell Babkin, and Lim and his associates *assume* that it is measured by the concentration of HCl in its secretion. This view is entirely erroneous, however. Since, in any given physiological situation, the concentration of HCl in the parietal fluid is fixed at an isosmotic value, this factor (4′) may be considered as a secondary, invariant characteristic of the secretion and consequently extraneous to these considerations. Instead, the energy expended by the cell in the act of secretion is determined by the amount of fluid which it pours out during that act. Were the composition variable, it also would enter into the calculation of the osmotic work—but this is not so, at least to any degree significant for our present purpose. Consequently, the degree of activity of the parietal cell must be measured by the volume of fluid which it pours out in unit time—and solely by this volume without particular regard to its acid concentration.

Thus, in order to show that the all-or-none law can be applied in this case, we must first of all establish quantitatively the nature of the relation between intensity of stimulus and volume of secretion. As yet, there isn't a single iota of evidence to indicate the nature of this relation. The rate of histamine absorption and the proportion of this substance which may be lost to other parts of the body following injection are both extremely variable. In fact, we are utterly unable to measure the amount of the stimulus which reaches the stomach, not to speak of its parietal cells, in any particular experiment. This situation makes any sort of quantitization of stimulus-intensity well nigh impossible at this time. The same situation obtains for the volume of secretion poured out per cell per unit time, that is, the number of cells which are active at any one time. In short, not only do we not have the necessary evidence to establish an all-or-none relation for the parietal cells, but we haven't even the methods by which to collect such evidence.

It may be argued that, in order to maintain the analogy with muscular contraction, the activity factor must include the acid concentration as well as the volume of secretion. Even so, it can be shown that the inclusion of concentration presents no difficulty and in no way affects the previous argument. Let us represent the degree of secretory activity by work in the special thermodynamic sense, and express it as the product of two factors, commonly designated as the capacity factor and the intensity factor. In accordance with this view, the activity of a parietal cell would then be measured by both the volume of secretion (capacity) and its HCl concentration (intensity); the product of the two equals the actual amount of acid elaborated in unit time, expressed as number of millimoles. The analogue for muscular activity would be the work of contraction, measured by the product of the load against which the muscle was pulling and the height through which it was raised. However, the analogy is not a perfect one, since both the volume and the concentration factors are determined by the secreting cell itself, whereas only the height of contraction is determined by the muscle fiber but the magnitude of the load is imposed on the system from outside it by the investigator.

Whether we choose this view of the problem or the previous one, based solely on the volume of fluid secreted, the fact still remains that as yet we have no way even of testing out the applicability of the all-or-none law to parietal secretion. Nevertheless, this problem is of importance both to the general physiologist who is interested in the fundamentals of cellular behavior, and to the scientifically minded clinician who is seeking to understand all phases of the secretory mechanism in his search for a way by which he can stop as well as start the process of acid secretion. We already know that increased stimulation does not change the concentration of HCl in the parietal secretion proper, but it is still an open question as to whether an additional stimulus increases the number of activity functioning cells or whether it induces a greater output of secretion from all of them simultaneously. This question regarding the all-or-none relation is intimately associated with other problems too: whether or not parietal activity is a continuous process; whether the parietal cell requires long or short periods of time for recovery from its secretory actively; whether the acid is formed as well as poured out under the influence of histamine, or whether it can be formed in the cell at any time and stored until its expulsion is induced by the proper stimulus. In order to make any headway with these problems, we must first of all introduce new experimental procedures, methods which are quantitatively precise and controllable. By comparison with the methods of the nerve-muscle physiologists, our own methods of study are still extremely crude, and we must emulate these investigators in regard to the mechanization of their techniques. Only by so doing can we hope to settle conclusively many of the physiological problems which

beset us in the gastro-intestinal field—among them the applicability of the all-or-none law to gastric secretion.

F. Hollander, New York City.

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DISTAL OR REGIONAL ILEITIS, ULCERATIVE ENTERITIS — NOT AN ENTITY*

IN 1932, Crohn, Ginzburg and Oppenheimer (1) believed that they had separated from the benign granulomata of the intestine, a subacute or chronic, necrotizing or cicatrizing process limited to the distal ileum. It occurred in the young, was of unknown etiology, was regarded by them as a pathologic and clinical entity and designated as "distal" or "regional ileitis."

Pathologically, the process involved 20 to 30 cms. of the terminal ileum. It ended abruptly at the ileocecal valve. The early lesions rarely seen, except at operation for appendicitis which condition it simulated, were never resected in the hope of spontaneous resolution. Here the affection appeared as soggy, oedematous, hose-like. The later stages, resected and studied more closely, showed varying degrees of mucosal inflammation, with eventual hyperplastic and exudative changes in the underlying structures. The lumen usually was encroached upon, the intestine above becoming dilated. Subsequently, repair in the form of fibrosis with stenosis occurred. Finally—possibly from pressure and from further trauma—a tendency to chronic perforation and fistula formation was noted. Microscopically, the lesion was seen as a non-specific inflammation affecting in varying degrees, first, the mucosa and, subsequently, the remaining walls with eventual fibrosis and multiple fistulae formation.

The clinical features were not unlike those encountered in ulcerative colitis. Subjectively, diarrhea, not so marked as in the latter, was the outstanding symptom. Loss of weight, fever and pallor were evident depending on the extent of the process. Objectively, a palpable mass—in the subacute and chronic stages—was constantly noted; anaemia, emaciation, a post operative scar of a previous appendectomy, and evidences of fistula formation and intestinal obstruction often were noted. The stool was positive for occult blood, roentgen phenomena, described by Kantor (2), indicated a deformed ileum frequently with dilatation above and a delay in motility, and negative rectosigmoidoscopy and roentgenology of the large intestine. No evidence was obtainable of pathogenic bacteria or parasites, intestinal tuberculosis, tumors, foreign bodies, Hodgkin's disease, or actinomycosis.

The clinical course was constructed upon the pathological anatomy noted above: the *first stage* simulated acute or subacute appendicitis; the *second*, that of ulcerative enteritis, established diarrhea a prominent symptom; the *third*, the stenotic phase, resulted in partial obstruction; and the *fourth phase* was that in which the persistent fistulae were seen. The clinical course was regarded as benign in that 13 of 14 cases were reported well, following surgery. In consequence, the treatment advised was surgical.

It must be granted that the finding of fourteen consecutive cases which, without exception, presented the above described picture, justified Crohn, Ginzburg and Oppenheimer in regarding the process as a pathological and clinical entity.

Close perusal of these data indicated that the claims to *entity* were based on two observations: *first*, the presence of a granulomatous process of unknown etiology, always confined to the terminal ileal segment, involving, but not extending beyond the ileo-cecal valve when the latter was intact, and not even invading the contiguous colonic tissue in the absence of the valve as when a sidetracking ileocolostomy was performed for relief; *second*, the presence of the characteristic clinical phases which were noted above.

A year after the communication of Crohn, *et al*, Harris, Bell and Brunn (3) reported an identical process involving the jejunum as well as the ileum. At the time this was questioned by Crohn (4) since the diagnosis was a clinical one, made at operation when there may be difficulty in distinguishing ileum from jejunum. Subsequently, the latter (5) confirmed this finding and the original concept was extended to include "jejunitis." Early in 1934, Colp (6) presented an identical, synchronous process affecting ileum and cecum and shortly thereafter P. W. Brown and co-workers (7) reported five cases involving the ileum, cecum and part of the ascending colon. Phillips (8) and Röpke (9) also described this process both in ileum and cecum. These concurrent small and large intestinal inflammations were granulomatous and hyperplastic and were not to be confounded with ileitis from extension of a severe colonic process where it is "destructive and denuding as it is in the colon" (5).

With regard to its unknown etiology, in 1935, Felsen (10) stated that he had traced eleven cases of acute and eleven of chronic distal ileitides to bacillary dysentery. Crohn (5) answered that he had encountered only "one positive agglutination against dysentery organisms in ileitis . . . ." He added that he was "not unwilling to deny absolutely the possible bacillary dysentery etiology of ileitis as well as of colitis." Therefore there come into being—subject to confirmation—at least two etiologic factors in this process, one possibly known and one or more still unknown. In this connection, it is conceivable that acute small intestinal and proximal colonic processes seen in epidemic food poisonings possibly due to staphlococcic and streptococcic endotoxins might very well become chronic in an occasional instance and might result in the lesions described above. Powers (11), Homans and Hass (12) and Clute (13), believed that there was a possible, although unproved, relationship of this involvement to recent or remote appendicitis. Even as to symptoms, the rapidly accumulating literature suggests their inconstancies. Thus, Probstein and Gruenfeld (14), in reporting three cases of acute regional ileitis, state that "no uniformity of symptoms (occur-

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red) which would facilitate preoperative recognition in the future."

In short, there has been described a granulomatous, hyperplastic process originally regarded as an *entity*, chiefly by virtue of its limited ileal location and unknown etiology, which has subsequently been found to involve the jejunum, cecum and ascending colon with identical pathologic and very similar but often dissimilar clinical manifestations, and which now seems to be due at least, in some instances, to *B. dysenteriae*. In consequence, it is believed that claims to *entity* cannot rightfully be maintained. On the basis of the critical analysis of the available data, it would seem that we are dealing with granulomatous, hyperplastic involvements which may be found anywhere in the intestinal tract. Its seeming relative propensity for the distal ileum may be due to stagnation at the ileo-cecal valve and the greater abundance of lymphatic tissue there than at other bowel segments, a factor favoring bacterial absorption (14).

However, these comments do not take away the credit from Crohn, Ginzburg and Oppenheimer as well as A. A. Berg, for clarifying the problem, and for making the profession more conscious of these processes.

Moses Paulson, Baltimore.

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THE OELGOETZ CONCEPTION OF ALLERGY

To the Editor, American Journal of Digestive Diseases and Nutrition,

I have followed with much interest the papers published by Oelgoetz and his co-workers, concerning the etiology, diagnosis and treatment of food allergy. The view set forth by these workers, if it is correct, is one of the most important things that has happened in Medicine; but their ideas are so new and revolutionary that I wish to raise the following questions:

1. Many ideas which Oelgoetz has proposed are at variance with accepted facts of the physiology of digestion.

2. Most of the Oelgoetz concept is at variance with all known facts of allergy.

3. If pancreatic amylase is not eliminated in the urine, what is the source of amylase found there?

4. The authors stated in their initial paper that the injection of an extract of foods causes an outpouring of enzymes into the blood stream. Why do they not use stimulating substances in the treatment of food allergy? Why do they recommend an extract of whole pancreas?

5. The authors state, on the basis of data presented only by themselves, that the pancreatic enzymes when taken by mouth, pass uninjured through the stomach, and are absorbed from the duodenum into the blood stream in the active state. This observation is of tremendous practical importance, if it proves true. Has this observation been confirmed by others?

J. O. Christ, M.D., Centerburg, Ohio.

Doctor Crist's letter was sent to Dr. Oelgoetz; his reply follows:

I will answer the questions raised by Dr. Crist in the order in which they were presented.

1. It is true that some of the basic ideas propounded by us, especially the importance of the blood stream and the serum enzymes in the physiology of digestion, are at variance with accepted facts. We can only state that in view of the incontrovertible nature of the facts upon which our concept is based, previous ideas concerning the physiology of digestion must be revised.

Walzer and his associates have shown that whole proteins are regular constituents of normal serum. Walzer's work proves our contention that proteins in all stages of digestion, all the way from acid and alkali metaproteins (whole proteins which can be identified biologically) to amino-acids, are regularly absorbed from the normal gastro-intestinal tract. This indicates that digestion is commenced in the gastro-intestinal tract, but that it is continued and completed in the blood stream.

We have shown that the blood always contains the three pancreatic enzymes in a constant concentration of 0.2 by the test which we have devised, and it is these free buffer enzymes which enable the individual cells of the body to correct their environment, *i.e.*, change whole proteins which are toxic and which cannot be used as food, to non-toxic split products which can be used as food. We have pointed out that *all* proteins, *all* carbohydrates and *all* fats are enzymatically and physiologically *similar*. It is only the presence of the serum enzymes—which are heterolytic and thus hydrolyze all foods and other substances which come within their sphere of activity—which prevents *all* of us from being food allergic *all* of the time.

2. It is not true that our concept of food allergy is at variance with all known facts of allergy. That whole proteins are toxic to cells, and that whole proteins are regular constituents of normal blood are biologic facts. We believe that we have demonstrated *the mechanism* by which the whole proteins normally present in the blood stream are prevented from reaching the individual cells in a toxic form which cannot be used as food.

By means of our test for determining the pancreatic function, we have demonstrated the underlying pancreatic secretory deficiency or achylia which is the cause of food allergy. It should be remembered that etiologically, there are different kinds of allergy; our work is concerned only with allergy to foods. But because foods constitute by *far the greater number*, the most frequent, and the most intimate of our contacts,

pancreatic dysfunction explains a high percentage of all cases of allergy.

3. The source of amylase found in the urine, as well as the enzymes found in every organ, tissue, secretion and excretion of the body, with the exception of the heart and brain, is the pancreas. Every fluid of the body is permeated with the pancreatic (serum) enzymes in a constant concentration. In short, the cells of the body live in a solution of pancreatic enzymes which prevent any food from reaching the individual cells without first having passed through this enzyme "bath." All substances which come within the sphere of activity of the pancreatic enzymes are thus detoxicated and split to a form which can be used as food by the cells. When, as a result of pancreatic hypofunction or achylia, the enzymes are present in reduced concentration or are entirely absent, whole proteins in varying quantities reach the individual cells and there follows the symptom-complex known as food allergy.

4. The injection of food extracts regularly causes an outpouring of serum enzymes, but only in normal animals with normal pancreases. In food allergy we always find a *minus* pancreatic index (pancreatic hyposecretion or achylia). The use of stimulating substances in the treatment of pancreatic hypofunction or food allergy would be equivalent to whipping a tired horse already out of breath; a tired pancreas (whether as a result of primary disease or secondary to other systemic disease) needs help in the form of *preformed* enzymes to supplement the inadequate gland. The administration by mouth of an active extract of whole pancreas is the rational therapy.

5. The fact that the pancreatic enzymes pass through the stomach and reach the duodenum uninjured, has been verified by Ivy of Chicago, who reported at the last meeting of the American Gastroenterological Association that he has recovered from the duodenum, in the active state, 51% of pancreatic enzymes taken by mouth. Ivy stated that there can no longer be any doubt concerning the activity of pancreatic extract orally taken.

Anton W. Oelgoetz, M. D., Columbus, Ohio.

SECTION IX—*Book Reviews*

(This section is open to contributions from any medical reader, whether or not a member of the Editorial Council).

The Eleventh Revision of the United States Pharmacopeia and the Sixth Revision of the National Formulary.

The U. S. P. XI, prepared by the Revision Committee of the 1930 Pharmacopeial Convention and the N. F. VI, prepared by the National Formulary Committee of the American Pharmaceutical Association are now published and became official standards on June 1. These books, which are legally recognized as authoritative standards, are of the utmost importance to the physician in his prescribing and administration of drugs.

There are many changes in each which are too numerous to mention in a brief review. The new Pharmacopeia contains 58 new items while 119 items have been deleted. The additions to the Pharmacopeia indicate the importance of New and Nonofficial Remedies, published by the Council on Pharmacy and Chemistry of the American Medical Association as the majority have been previously recognized and described in that volume. Most of these additions have been wisely selected although some physicians will wonder why certain substances have been made official and others not. For example, Novosurol has been made official as Merbaphen, while Salyrgan, a generally preferred preparation, is not included. There are reasons for such discrimination (*i.e.* that monopolized substances are not admissible to the U. S. P); such facts are not generally known by physicians.

There is a number of changes in official names, in spelling, and in standards of purity, but fortunately very few in the composition and therefore dosage of the compounded preparations.

The N. F. VI has adopted the general style of the Pharmacopeia, a change which is a distinct improvement. This book contains 150 new items (of which 80 were deletions from the U. S. P. X) while 319 items were deleted. Amongst the important additions for the prescribing physician is Iso-Alcoholic-Elixir, which is an alcoholic vehicle which may be prescribed by name leaving the alcohol concentration to be adjusted appropriately by the pharmacist.

A. C. Ivy, Chicago.

OBITUARY

James Tate Mason: An Appreciation

JAMES Tate Mason came from a sturdy ancestry in the Old Dominion. His grandfather, Capt. Claiborne Rice Mason, was a self-educated man, and was a pioneer railroad contractor who constructed the greater part of the Chesapeake and Ohio, and much of the old Virginia Midland Railroad. He was one of Stonewall Jackson's engineers during the Civil War. In fact the firm of Mason, Rinehart & Co., has existed



JAMES TATE MASON
1882-1936

for more than a hundred years under various names, but always with a Mason in the firm, and at the present time as the Mason-Walsh-Atkinson-Kier Company is building the Coulee Dam in the State of Washington, the largest construction project ever undertaken by man.

Captain Mason's son, Dr. Claiborne Rice Mason, was also under Stonewall Jackson, was wounded and captured, and was kept as a prisoner of war at Elmira until the surrender at Appomatox. He was paroled and became a student at the University of Virginia, and later graduated in Medicine at the Jefferson Medical College in Philadelphia. He later married Mary Moore Woolfolk of Orange County, Virginia, a member of a prominent colonial family. From this union the only child was James Tate Mason, born May 20, 1882, at Lahore, Orange County, Virginia, where his father was a practitioner.

Young Tate Mason went to the Locustdale Military Academy when fourteen years old and was unusually well liked. He soon demonstrated remarkable athletic ability, particularly in baseball. He entered the University of Virginia Medical School in 1901 and made an enviable record as regards both athletics and popularity. He was a star on the baseball team and was beloved by his fellow students—in fact to the day of his death he was constantly in demand by former college friends. His scholarship was only average, but in spite of this he was as well liked by his professors as by his classmates. Even today at the University of Virginia his wholesome good fellowship and lovableness are a tradition.

In his medical schools days Mason served during summer months as assistant to Colonel Frazier, owner and manager of the Rockbridge Alum Springs. There were no vacations for him, as was so often the case in Virginia on account of the poverty of the early 1900's. Each summer he entertained his parents for a few weeks at the Rockbridge Alum Springs. His radiant and winning personality as a boy proved a valuable asset and made the Colonel so fond of him that when Colonel Frazier died thirty years later he made Doctor Mason heir to half of his small estate. Such devotion was Doctor Mason's good fortune all his lifetime, for no man ever made stauncher friends or more of them.

He graduated from the University of Virginia in 1905, took the Virginia State Board immediately, and then began a two-year service at the Philadelphia Polyclinic, now known as the Postgraduate School of the University of Pennsylvania. Always his rare personality made friends. After this he was Resident at the Municipal Hospital of Philadelphia for the Treatment of Contagious Diseases.

In the spring of 1907 the Pacific Coast Steamship Company built two ships at Camden, New Jersey. One of these, *The President*, was going around the Horn, and young Mason, just through with internships, applied for a place as ship's surgeon. The trip was to pay a hundred dollars and a ticket home from Seattle. On arrival in Seattle, after his first and only adventure as a mariner, he found the Northwest July at its best —a new country, a wonderful climate—and his youthful enthusiasm and lack of other plans for the future,

together with total assets of less than fifty dollars, made him seek a job. Within two weeks he found a position as local surgeon for the Pacific Coast Coal Company at Franklin and later at Black Diamond, Washington. There he spent two years, actively engaged in looking after the miners and their families. He always loved people—and these new people, with their trials and their babies, felt that the new doctor was a Godsend. They loved him. He returned to Seattle in 1909 to engage in practice, and the miners in trouble still came to him for the rest of his life. The old timers at Black Diamond loved him so much that many tearfully attended his funeral twenty-seven years later.

On taking up practice in Seattle he rapidly acquired a large but not particularly remunerative following. He worked hard, made friends everywhere, but had little income. Within a few months he welcomed the opportunity to become physician to the County Jail, as well as to the family of the Sheriff, the late Robert Hodge.

In January, 1911, he married Laura DeWolfe Whittlesey. Such new responsibilities spurred him to greater professional effort, particularly the arrival of his first-born, James Tate Mason, Jr., and later a daughter and another son.

He was elected Coroner of King County and took advantage of this opportunity to have a large autopsy experience and to start an Anatomical Club with his friends. The Anatomical Club later became the Seattle Surgical Society, now a flourishing organization. In 1914 he was made Superintendent and Surgeon of the King County Hospital, a position which he held until 1922. These eight years gave opportunity for a tremendous surgical experience. He took advantage of it with such deligence that, with visiting eastern surgical centers each few months, he became a finished surgeon. He was an original and unorthodox thinker, and made up for his lack of early schooling by phenomenal ability to observe and get the best out of what he saw and heard.

In 1917, Doctor Mason organized a partnership which later, with additions, became The Mason Clinic. In 1919 he and his associates organized and built the Virginia Mason Hospital, of which he was Chief Surgeon and President of the Hospital until his death.

Doctor Mason's ability as an organizer was abundently shown in his hospital adventure. A private hospital is always an adventure, and the vicissitudes of high finance were beautifully demonstrated. Financial backing was not to be had for such a venture. He finally sought aid from a mortgage company. The president told him, "Yes, we'll loan you the money, but you won't want it because it will cost too much." This was a terrible set-back, and Mason's face showed it. Suddenly the president said, "Tate, I'll see that you get your money, and I'll have some fun, too, if you will do exactly as I say. We will loan you the money at 8 per cent and 10 per cent commission, and you can have it right now—but of course you won't take it. Leave this office and drop in at your bank. Tell them I have promised to let you have your money. Tell the next bank you know the same story. Tomorrow see a couple of other concerns about borrowing, and, if I am a good guesser, you will get your money on reasonable terms and I will get a lot of satisfaction. The lender won't make a cent, and I'll have my joke."

It was done. Next day the money was obtained at normal interest, and the Virginia Mason Hospital was launched. A few years later Doctor Mason had the pleasure of burning the bonds in favor of a reasonable savings bank mortgage.

This new venture on so little capital was part of his life's ambition. He loved it and wanted it to prosper. Gradually more and more work arrived, and he became as busy in his own hospital as he had been at the County Hospital.

He was appointed Secretary to the Surgical Section of the American Medical Association, and after this time honors came fast. He was one of the founders of the Pacific Coast Surgical Association, a member of the Western Surgical, Southern Surgical, and American Surgical, as well as the Northwest Surgical and the Seattle Surgical Society. He was a member of the College of Surgeons, the American Medical Association, the Washington State Medical Association, and King County Medical Society. He was past president of the American Association for the Study of Goiter, 1930, and the Pacific Coast Surgical Association, 1931. At the time of his death he was consulting surgeon to the U. S. Marine Hospital, American Mail Line, Alaska Steamship Line, and the Northern Pacific Railroad. He was also President of the American Medical Association, surviving his inauguration *in absentia*, to this high office by five weeks.

A busy and active professional life, with his phenomenal ability to make and hold friends and patients, and much professional travel, began to take its toll. He was so much beloved that he was always a toast. As a story-teller he excelled, and as a speaker he had a unique style that everyone liked. Nurses adored him and brought him all their troubles—and he always had time for the ladies. He rarely spoke a cross word to anyone—in nearly twenty years' association he never had an argument with his partners. Yet at times he felt keenly any suggestion of a slight. A partner on one occasion had exploded on learning of a false accusation by a fellow practitioner and had announced that he was "going to tell that fellow what I know about him." Doctor Mason said, "Don't do it. If you ever need to use what you know about him it won't do any good if he knows that you know it"—showing the kindly politician that he was. Doctor Mason was deeply emotional inside, a fact known only to his close friends. He loved people, all people except a few, and the few usually never found out how he felt. He was kind and sympathetic and for this reason heard innumerable troubles of a non-professional nature. He usually saw a funny side to every situation, and always had a story to fit the occasion.

In 1932, he had a nervous breakdown and was out of the office for months. His blood pressure was up a little, and this disturbed him. At times he complained of extrasystoles and chest pains. He felt that he suffered with angina, though his partners could never agree with his own diagnosis. He recovered to the extent that he resumed his activities completely, though at times a little nervously depressed. He had been for years delegate from the Surgical Section to the House of Delegates of the American Medical Association, and this led to further political interest. In 1935 at Atlantic City he was made President-Elect of the Amer-

ican Medical Association. In November of that year he made a speaking tour for the Association, delivering a number of addresses before large audiences. He came home tired.

On Christmas Day, 1935, he went to pieces nervously and was admitted to his own hospital. Nervous symptoms predominated, and he went through a very trying time for a number of weeks. In March, he returned home, feeling much improved. He was struggling hard to regain his health in order to be inaugurated President of the American Medical Association.

After being home for about three weeks, on April 6th, he lunched with his partners and after lunch announced, "Boys, I believe I'm well. I am going to put in a full afternoon in the office"—and he did, admitting several patients for operation. That night lightning struck—an arterial thrombosis in the left leg—and forty-eight hours later, a left-sided paralysis (right cerebral thrombosis). Amputation of the leg followed, but there was no recovery. Five days after operation right arterial thrombosis and gangrene of the right leg—later other areas of gangrene—and suffering beyond human endurance. The last few weeks were lengthened and comforted by morphine and by wonderful nursing—and a devoted family who stayed by him constantly to the bitter end. The last weeks of his life were widely publicized. His inauguration *in absentia*, his listening by radio to the Kansas City meeting, the unanimous action of the House of Delegates to over-rule the ruling of the Judicial Council and to inaugurate a dying man as President—all are now matters of sad history, tributes by loving and grieving friends to comfort one about to die, and to help his family endure their sorrow.

Tate Mason never gave up hope of recovery or admitted the inevitable. He joked with his nurses and sent messages to his friends. Five days before his release from suffering he caused the writer, his closest associate, to make a rushing and emotional exit from the sick room. "John, I can't walk much this summer without any legs, and I love to be out of doors. Take me out a lot with you on your boat this summer."

J. M. B.

SECTION XI—*Societies, Programs and Proceedings*

AMERICAN PROCTOLOGIC SOCIETY

The American Proctologic Society held its annual meeting in Kansas City on May 11th and 12th, with an attendance of 175. The following were elected to Associate membership:

Dr. Harry W. Christianson, Minneapolis.

Dr. C. C. Hickman, Lincoln, Nebraska.

Dr. Lester P. Johnson, Ann Arbor.

Dr. Kenneth E. Smiley, Los Angeles.

Dr. Tom E. Smith, Dallas.

Dr. Victor K. Allen, Tulsa; Dr. Malcolm R. Hill, Los Angeles, and Dr. George H. Thiele, Kansas City, were elevated to Fellowship in the Society. Dr. Louis J. Krouse of Cincinnati was made a Fellow Emeritus.

The following officers were selected for 1936-37:

President: Dr. Marion C. Pruitt, Atlanta.

Vice-president: Dr. Clement J. DeBere, Chicago.

Councillors: Dr. Edward G. Martin, Detroit; Dr. Martin S. Kleckner, Allentown, Pennsylvania.

Secretary-treasurer: (re-elected) Dr. Curtice Rosser, Dallas.

The next annual meeting will be held in Atlantic City in June, 1937, with Dr. Homer I. Silvers as Chairman of Arrangements.

Curtice Rosser, M.D., Dallas, Secretary.

SECTION XII—"*The Clinic*"

Extra-Pancreatic Hypoglycemia*

By

JOHN FRANCIS BRIGGS, M.D.†

and

HARRY OERTING, M.D.‡

ST. PAUL, MINNESOTA

THE dramatic symptomology of the hypoglycemic state makes this symptom complex easy to recognize. Unfortunately, however, the symptoms alone do not disclose the underlying etiology of the attack, and it is this knowledge that is so essential in prescribing the proper treatment for the individual case. Literature is quite complete with the present knowledge of this syndrome, but it deals largely with the pancreatic origin of hypoglycemia. Recently one (1) of us emphasized the necessity of recognizing extra-pancreatic forms of hypoglycemia, and for this reason we take the liberty of reporting two fatal cases of extra pancreatic hypoglycemia.

REPORT OF CASES

1. Mr. H. S., a white male, 68 years of age, entered the Ancker Hospital on September 14, 1935. At the time of admission he complained of inability to move his legs, a feeling of generalized weakness which had persisted for three weeks, as well as a loss of thirty pounds in weight. He described his present condition as being the result of eating "rotten" hamburger in August, 1935. Shortly after this meal he developed crampy colicky pains which were limited to the epigastric region. After one week of this pain, nausea and vomiting occurred. The vomitus was foul smelling and green in color. He noticed that the eating of solid foods made the condition worse and when he limited his diet to liquids he obtained marked relief. The nausea, however, kept recurring and he noticed that his weight was less and that he had difficulty in walking because of his generalized weakness. Two days before his admission to the hospital, vomiting became persistent and he was forced to seek medical attention.

His past history and family history are irrevalent to the present discussion.

Physical examination revealed an extremely emaciated white male who appeared more like a man eighty years of age rather than his stated age of sixty-eight years. Temperature 98. Pulse 60. Head, alopecia totalis. Eyes, there was a definite arcus senilus present but the eyes were otherwise normal as regards to reflexes and fundus examination. Ears, canals were occluded with wax and the drums were not visible. Nose, negative. Mouth, the tonsils were deeply embedded in the fossae. His tongue was coated, but showed no atrophy. There was marked pyorrhea and dental caries. Many of his teeth were missing. Neck, thyroid was normal. No lymphadenopathy. Chest, examination of the chest was so handicapped by the marked emaciation that the findings were unreliable and will not be reported. Heart, tones clear. Apex beat is in the fifth interspace in the midclavicular line. Rate normal. No murmurs heard. Blood pressure was 86 over 56. Abdomen, examination revealed nothing abnormal. Hernial rings, pulsating masses could be felt in both inguinal canals. Rectum, negative. Genitalia, negative. Reflexes, negative. Extremities, negative.

Diagnostic impression on admission was (1) Probable gastro-intestinal malignancy, (2) bilateral inguinal hernia, (3) cachexia and inanition.

On September 14, 1935, at 1:30 p.m. the patient suddenly lapsed into coma. His respirations were rapid and shallow. The blood sugar taken at this time revealed 30 mg. of sugar per 100 c.c. of blood. 50 c.c. of 50% glucose were administered intravenously. After 30 c.c. had entered the vein the patient regained consciousness and appeared brighter. One hour later 1000 c.c. of 5% glucose and saline were given intravenously and the patient appeared normal. At 3:30 p.m. of the same day the patient again reverted to a comatose condition at which time the blood sugar level was 49 mg. per 100 c.c. blood. Despite heroic measures the patient did not respond and died at 4:00 p.m. on the day following admission.

Laboratory examination, sputum negative for tuberculosis. Gastric analysis, free hydrochloric acid 20 degrees; total 70. Hemoglobin 30%. Red blood count 2.9. White blood count 7,,850. Blood Chemistry, creatinine 1.8 mg. Urea nitrogen 32.2 mg. Calcium 7.5 mg. icterus index .10. Urine examination was negative. X-rays of the chest was negative. Basal metabolism, minus fifteen.

The *pre-mortem diagnosis was:* I. Hypoglycemia, secondary either to (1) pituitary disease, (2) pancreatic disease, (3) carcinomatosis. II. bilateral inguinal hernia.

Post mortem examination was done on the following morning, and in order to avoid repetition, only the essential portions of the necropsy will be reported. *Examination of the gastro-intestinal tract* revealed an ulcerated carcinoma on the lesser curvature in the region of the pylorus. The edges were round and elevated. In addition a healed peptic ulcer was found. Examination of the lungs revealed a bilateral bronchial pneumonia, as well as a bilateral hydrothorax. The liver showed marked atrophy and weighed only 800 grams. The rest of the necropsy showed nothing of note. *Microscopic examination* of the pancreas showed the organ to be normal. Repeated sections revealed no disturbance in the islands of Langerhans.

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Submitted February 24, 1936.

Section of the hypophysis revealed a slight degree of atrophy, but the histology was otherwise normal.

Summary: It appears obvious that the pancreas only played a secondary role in this instance of hypoglycemia. It is our belief that the marked cachexia and inanition which was secondary to the carcinoma of the stomach was sufficient to deplete the glycogen reserve in an already injured liver. The influence of liver atrophy upon the storage of glycogen is obvious, and no doubt played the greatest factor in producing this case of hypoglycemia.

2. The second case is that of an adult white male, L. F., age 27 years, who entered the hospital in December, 1934. At the time of admission to the hospital he complained of nausea, general weakness, canker sores in his mouth, headache, and pigmentation. He stated that he was perfectly well until about fifteen months ago when he was working for an uncle on a farm in Preston, Minnesota. He first noticed that the skin of his face, arms, and back of his hands became dark. He also noticed a dark band around his lower abdomen. This color change was first noticed by his uncle. He then began to lose weight rapidly. He weighed 158 pounds and within three months he lost about fifty pounds. Thanksgiving day of 1933, the patient developed nausea but did not vomit. He developed vertigo and marked general weakness. He consulted a doctor in Preston, who treated him until Easter of 1934. Patient then came back to Saint Paul and started going to the Dispensary. He was told that his blood pressure was low, and was given two pink capsules *b.i.d.* He was treated so until July, 1934, with marked improvement. The symptoms disappeared and the skin cleared up. He was told that his blood pressure was about normal. He then stopped treatment. About three days ago he developed nausea, general weakness, and canker sores in the mouth. He has had a headache for the past three days. He vomited on the day of admission and noticed a slight amount of blood in vomitus. He coughs occasionally but brings up very little sputum. His mother is confined to the Ancker Hospital because of pulmonary tuberculosis. Patient had a chest plate at the Wilder Dispensary in July, which was negative.

Past history: Past health good. Previous illness: measles, whooping cough, scarlet fever, mumps, and chicken pox. He has had no operations. Venereal disease denied.

Past history by systems: Head; continuous headache for the past three days. He has had vertigo. Eyes; no diplopia. Occasional blurring. Ears; no earaches. No discharge. Nose; no obstruction. No discharge. Mouth and Throat; occasional sore throat. Has one at the present time. Canker sores in mouth. Teeth need attention. Chest; occasional cough. No sputum. No hemoptysis. No retrosternal or precordial pain. Dyspnea with present attack. Also palpitation. No edema of ankles. Gastro-intestinal; appetite good previously. Poor with present attack. No food distress. No vomiting except as noted above. Bowels normal. Has noticed some red blood once in past few days. Genito-urinary; no dysuria. No hematuria. No frequency. No incontinence. Urinates three or four times a day, once at night. Habits; smokes almost 20 cigarettes per day. Did not drink during past six months. About a year and a half ago he drank a lot of alcohol for about three months, sometimes one quart a day. Weight; 155 pounds 1 year ago. U. 135. P. 135.

Marital history: Single.

Family history: Father, age 65, living and well. Mother, age 51, has tuberculosis. Three brothers living and well. Two sisters living and well. Aunt, mother's sister, died of tuberculosis. No other tuberculosis.

Physical examination reveals a white male, age 27 years. Fairly well developed, presenting a rather dark pigmented skin and possibly somewhat undernourished. Head; scalp negative. Eyes; pupils equal and regular. React to light and accommodation. Occular movements normal. Sclera slightly darkened. Ears and Nose; negative. Face; appears dark with dark pinhead sized melanin spots scattered over entire face. Never had these previously. Mouth and Throat; pharynx somewhat injected. Tonsils somewhat enlarged. Few small areas of pigmentation on buccal mucosa, especially on the right side. Teeth are in fair condition. Neck and Glands: thyroid not enlarged. Cervical and axillary glands not palpable. Chest and Lungs; depression in lower sternum. Expansion fair. Dullness in both apices posteriorly. Suggestion of few rales in left apex. Breath sounds are normal. Heart; not enlarged. Tones normal. No murmurs. Regular rhythm, but somewhat rapid, rate about 90 per minute. Blood pressure 82 over 56. Pulse 90. Abdomen; no masses. No tenderness. Liver and spleen not palpable. Skin darkened with several pigmented pinhead sized areas. Genitalia; negative. No abnormal pigmentation. Extremities: upper, definitely pigmented with several pinhead sized areas of pigmentation. No definite pigmentation of palms. Lower, very little pigmentation present.

Laboratory examination: Urine; appearance, amber. Reaction, acid. Specific gravity 1.020. Albumin, negative. Sugar, negative. Hyaline casts, occasional. Leucocytes, occasional. Erythrocytes, negative.

Examination of blood: Hemoglobin, 102%. Red blood count 5,680,000. White blood count 8,300. Polymorphonuclear 48% per 100 c.c. of blood. Lymphocytes 46%. Monocytes 1%. Eosinophile 4%. Basophile 1%. Creatinine 68 mgs.

X-ray examination of the chest was negative for calcification, left root.

Diagnostic impression on admission was: (1) Addison's disease; (2) possible pulmonary tuberculosis.

On December 7, 1934, the patient complained of headache and nausea. He vomited once during the a.m. His pulse and heart tones were weak. Blood pressure was 78 over 50. Patient felt weak. At 8:30 p.m. patient began to yell suddenly. He picked up a pitcher of water and threw it against the wall. He stated that three men came into his room and suddenly hit him on the head. He then took the pitcher and hit one of the men on the head. Patient seemed wild and confused and stated that everything was going wrong. He threw himself wildly around the bed. He was given three grains of luminal and he spit it out on the floor. *Blood sugar 48 mg. per 100 c.c. of blood.* He was finally given sodium luminal grains IV by hypodermic. The above symptoms can only be explained on a hypoglycemic basis. Patient became quiet. At 11:00 p.m. he again went on a rampage. He got out of bed and walked into other patient's rooms. He was then placed in bed in restraints. Patient was not oriented and seemed to think that he was in Rockford, Illinois. He had a horizontal nystagmus. He was given morphine sulphate grains 1/6 and 50 c.c. of 50% glucose were administered intravenously, after which the patient seemed to quiet down somewhat. On December 8th at 10:00 a.m. the patient seemed rational again, but complained of being very cold. His pulse was very feeble. Blood pressure was 58 over 30. Adrenalin M. ten was given every half hour, four times. At 2:00 p.m. 1000 c.c. of normal saline were administered intravenously. His blood pressure was 60 over 30. Blood sugar level at this time was 32 mgs. per 100 c.c. of blood. At 6:10 p.m. the patient expired.

Diagnosis: (1) Hypoglycemia. (2) Addison's Disease. (3) Atrophy of the adrenals.

Necropsy was performed the morning following death. The only essential finding at the necropsy was the complete atrophy of both adrenal glands to such an extent that

it was almost impossible to identify them in the surrounding tissue.

Microscopic examination of the adrenals revealed very few cells and almost complete replacement of the adrenal by fat tissue. Microscopic examination of the pancreas showed the islands of Langerhans to be normal.

Summary: The marked influence of the adrenals upon the maintenance of a normal blood sugar level is well known. The atrophy of the adrenals was unquestionably the only factor operating in this instance to produce hypoglycemia.

FINAL CONCLUSIONS

Two fatal cases of hypoglycemia are reported wherein the factors producing the disease were of extra pancreatic origin, namely cachexia and atrophy of the liver in the first, and bilateral atrophy of the adrenals in the second.

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Regional Ileitis

By

F. GREGORY CONNELL, M.D.*
OSHKOSH, WISCONSIN

PATHOLOGY and abnormal function of the various divisions of the gastro-intestinal tract have been given much study, but that portion extending from the ligament of Trietz to the ileocecal valve has been comparatively neglected.

In the upper areas: Ileo mesenteric ileus, retro peritoneal herniae, diverticula, primary jejunal ulcer, benign or malignant tumors, disease or calcification of mesenteric glands have been described.

In the lower area: In the terminal ileum, proximal to the valve, disease processes frequently have been overlooked and when discussed, have been greatly confused, probably because of the adjacent appendix.

They may be divided into: (a) Inflammatory: specific or non-specific ileitis, with or without ulceration, stenoses, adhesions or adenopathies. (b) Neoplastic: benign tumors, carcinoids or malignant carninomata. (c) Congenital: Meckel's diverticulum, developmental defects, atresias, or "adhesions."

The carcinomata and the carcinoids (b) have been given recent careful study. The congenital defects (c) that may occur in the ileocecal region are well understood.

From the heterogenous group (a) of inflammatory lesions the so-called "benign non-specific granulomas," Crohn, Ginsberg and Oppenheim have isolated a clinical entity, described as "—a disease of the terminal ileum, affecting mainly young adults and characterized by a subacute or chronic necrotizing and cicatrizing inflammation of all the coats of the ileum which frequently leads to stenosis of the lumen and is often associated with fistula formation and a tumor mass in the right lower quadrant."

This was, at first, thought to occur only in the terminal ileum and was called "terminal ileitis," but with further study it was found in other locations of the small bowel and was therefore termed "regional ileitis."

The etiology is unknown. The affection occurs frequently in young males with a long history of fever, diarrhea, loss of weight and anaemia, malaise, abdominal pain and a clinical picture resembling non-specific ulcerative colitis, with later usually a mass in the right iliac fossa and intermittent intestinal obstruction.

X-ray barium meal, if carefully observed through the small bowel at frequent intervals, may give the diagnosis.

The barium enema, because of the situation of the lesion, will usually fail to reveal the pathology.

Because of the recent publications of numerous articles discussing the pathology, the unknown etiology, the clinical histories, physical and X-ray findings, differential diagnosis and treatment, they will not be repeated here.

CASE HISTORIES

Brief summaries of three such cases follow:

Case 1. R. O., Male, single, laborer.

History: For 14 years attacks of abdominal cramps, "gas," nausea, vomiting and constipation.

July 15, 1930. First hospitalization: *Operation* for "chronic appendicitis." No improvement.

A *second operation,* enterostomy, was performed.

August, 1934. The sixth admission to hospital for practically the same chain of symptoms. For the past year he had been an inmate of a sanatorium and was considered as having a tuberculous peritonitis.

September 3, 1934. Third operation: The diseased terminal ileum was removed and enteroenterostomy was performed.

November 6, 1934. The enterostomies were closed, one in midline and two in right iliac fossa.

August, 1935. Symptom free.

Case 2. A. M., Female, age 47 years, married, housewife. 5 children.

History: November 6, 1928. First hospitalization. For about a month had had diarrhea, no gross blood, no pain. Loss of weight. Previous history negative except for occasional gas after meals. Diagnosis, "Colitis." November 28, 1928. Discharged "Improved."

May 17, 1929. Second hospitalization. Continued symptoms. Diagnosis, "Ulcerative colitis." *First operation:* Ileo-ileostomy followed by second stage enterectomy of six

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Submitted April 9, 1936.

inches of terminal ileum. Followed by fairly satisfactory condition to June 4, 1934.

June 4, 1934. Third hospitalization. Tender mass baseball size in right iliac fossa. Nausea and vomiting, diarrhea, loss of weight.

June 6, 1934. First stage of Mikulicz's operation. Recurrence of tumor at site of anastomosis in terminal ileum.

June 13, 1934. Second stage of Mikulicz's resection.

July 24, 1934. Discharged from hospital in good condition, but with small intestinal fistula.

December, 1934. Present condition satisfactory, but has a persistent fistula.

July, 1935. Closure of fistula.

Case 8. Mrs. N. B., Female, married, age 29 years. 4 children, 2 miscarriages.

History: This case has been unclassified in my files since 1912, until the subject of "terminal ileitis" now serves as an excuse for including it with the two previous cases.

1905. First hospitalization (elsewhere). Appendectomy in 1905 for "chronic appendicitis." Five or six attacks in two years before operation. Was symptom-free for one year after operation. For the next six years attacks of intestinal obstruction three to five times a year, accompanied by pain and swelling in right iliac fossa.

June, 1912. Second hospitalization. *Operation:* Terminal ileum thickened and enclosed in fibrous sac. This parchment-like membrane was removed and ileum straightened out and omentum placed over bowel.

September, 1912. Third hospitalization. Symptoms of chronic obstruction. *Operation:* Ileo-sigmoidostomy.

October 15, 1912. Fourth hospitalization. Acute intestinal obstruction. *Operation:* Enterostomy.

June, 1913. Fifth hospitalization. Lower ileum markedly improved. Localized jejunitis, the most striking finding at operation. *Operation:* Gastro-enterostomy, excluding the thickened convoluted jejunum. Improved to November 13, 1913.

November, 1913. Sixth hospitalization. *Operation:* Resection of terminal ileum (serosa red, congested and rough, wall thickened, mucosa not ulcerated) and resection of ascending and half of transverse colon. The previous gastro-enterostomy and ileosigmoidostomy were functioning normally.

Up to 1925, Mrs. B. was quite comfortable with occasional digestive upsets after which she was lost track of.

SUMMARY

Three cases of regional ileitis are reported.

Credit for a real advance in gastro-intestinal disease —the recognition of terminal or regional enteritis— is due Drs. Crohn, Ginsburg and Oppenheim.

The cause is, as yet, unknown but with further study probably will be discovered.

The condition must be thought of in all cases of chronic diarrhea or constipation and in atypical abdominal disease.

In X-ray barium "progress" meals, more frequent examinations, at shorter intervals, and at different angles, may reveal abnormalities in the small bowel that would otherwise be overlooked.

Barium meal should always be supplemented by barium enema and *vice versa*, enema checked by "progress" meal.

Large incision and careful examination of terminal small bowel are indicated in all laparotomies for chronic abdominal symptoms, especially in cases operated upon for so-called "chronic appendicitis."

"Tumors" of the lower small bowel are not necessarily cancer or "carcinoids."

Spontaneous fistulae between abdominal or pelvic viscera may not be malignant.

Extensive resection, into the normal bowel, is usually successful.

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Gastro-Intestinal Bleeding in Disease of the Liver and Biliary Tract

By

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NEW YORK, NEW YORK

HEMATEMESIS or melena, occurring in the course of liver and biliary tract disease, is usually associated with a ruptured oesophageal varix or the bleeding tendency of jaundiced subjects. Less commonly hemorrhages from the gastro-intestinal tract occur on a different basis and these instances deserve consideration. A classification of the types of gastro-intestinal bleeding associated with liver and biliary tract disease has therefore been attempted.

Bleeding from a varix, peptic ulcer or malignant disease of the biliary tract has been ruled out in the cases here reported. Our cases emphasize the fact that occult and gross bleeding in the intestinal tract may occur in acute gall bladder disease without jaundice and in damage of the liver parenchyma without a general bleeding tendency.

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Submitted February 6, 1936.

CASE REPORTS

Case No. 1. R. B. Subacute Yellow Atrophy of the Liver. Melena.

A female, aged 57 years, with a history of recurrent myalgias and arthralgias, recently developed severe pain in the left sacro-iliac region radiating to the left thigh

and leg. For four weeks she received intravenous injections of sodium iodide and intramuscular injections of Aolan, a milk preparation. She also received coal tar analgesics and one five grain tablet of cinchophen. One week before admission, seven weeks after receiving the therapy, she noted icterus, dark urine, anorexia, epigastric distress, and pale yellow stools.

Physical examination revealed an intense icterus. The liver was enlarged two fingers breadth below the costal margin. The spleen was not palpable. There was marked tenderness over both sacro-iliac regions. Bile was present in the stool and urine. X-ray examinations of the gall bladder and gastro-intestinal tract proved negative. Leucocytosis of 17 and 22,000 cells per cubic millimeter of blood was present despite clinical improvement. Tyrosine was demonstrated in the urine by the author's tyrosinase method. Biliary drainage indicated the presence of frank blood with some clots without trauma.

Chemical examination of the blood showed a prompt positive Van den Bergh reaction and bilirubinemia of 23 mg. per 100 c.c. The icterus index was 200. The bilirubinemia dropped to 16 and finally 14 mg., the icterus index to 140. The total cholesterol was 210, the ester fraction being 125 mg. per 100 c.c. The total, eventually dropped to 125, the ester fraction to traces.

Despite intravenous and oral administration of large amounts of carbohydrate the patient lapsed into coma. Hyperglycemia (350 mg.) and glycosuria (5 per cent) developed and were controlled by insulin therapy. The size of the liver decreased terminally. Edema and ascites appeared. She vomited coffee ground material and died in coma one month after admission to the hospital.

Necropsy showed the presence of a subacute yellow atrophy of the liver, subacute pancreatitis, ascites, hydrothorax and superficial erosions of the stomach. Histopathological examination of the liver revealed widespread destruction of liver tissue with a large amount of necrotic granular debris, pyknotic nuclei, and large areas of hemorrhage. Islands of liver cells adjoining the necrotic areas showed similar but less pronounced changes. These islands of relatively less severely injured cells were enveloped by bands of stroma containing plasma cells, round cells and polymorphonuclear cells, and by areas of hemorrhage and by portal spaces.

The presence of frank blood in the biliary drainage fluid prompted the diagnosis of an ulcerating malignant lesion of the papilla of Vater. The histological demonstration of pools of blood in the necrotic liver parenchyma established the possibility of this local source of bleeding in this type of case as severe parenchymal liver damage.

Case No. 2. A. G. Chronic Cholecystitis; Cholelithiasis; Choledocholithiasis; Melena; Hematemesis; Cholecystectomy; Choledochostomy.

A female, aged 40, a housewife, entered the hospital for relief from attacks of pain in the right hypochondrium, 20 years in duration. 20 years ago, an attack had been followed by transient jaundice. In the preceding 6 months, there had been increasingly severe attacks of pain in the right hypochondrium radiating to the back and shoulders and accompanied by vomiting. Two months before admission, icterus, dark urine and pruritus developed. 24 hours before admission she vomited a large amount of black fluid and had tarry stools thereafter.

Examination showed the presence of icterus and tenderness in the right upper quadrant of the abdomen. The rectal temperature was 100.4 degrees Fahrenheit. Chemical study of the blood indicated an icterus index of 22, a bilirubinemia of 0.9 mg. per 100 c.c.. The Van den Bergh reaction was delayed, direct, positive. The total cholesterol was 190 and the ester fraction decreased to 36 mg. per 100 c.c.

The intestinal bleeding prompted several diagnoses: ulcerating malignant disease of the papilla of Vater, ulcerating choledocholithiasis, and bleeding peptic ulcer. A plate of the abdomen revealed gall stones by X-ray. The Graham test failed to visualize the gall bladder. X-ray examination of the intestinal tract disclosed no abnormality.

Many gall stones were found at laparotomy. The bladder was removed and a single stone, the size of an olive pit was removed from the common bile duct together with much detritus. The papilla and the ducts were freely patent. A source for the bleeding was not uncovered. The stomach and duodenum were normal to palpation. The common duct was drained for nine days. The bleeding did not recur. The patient was observed for one year following operation.

Peptic ulcer was ruled out by X-ray and laparotomy. There was no hemorrhage in the gall bladder or bile ducts. There was no evidence of bleeding tendency before or after operation. There was no violent retching or vomiting. The vomiting was probably caused by the accumulation of blood in the stomach. The cause of bleeding in this case must be recorded as undetermined.

Case No. 3. Cholelithiasis, Chronic Cholecystitis, Acute Hemorrhagic Cholecystitis, Hematemesis.

S. S. A female, aged 64, a housewife, suffered from arthritis for 15 years. For a year prior to admission to the hospital the patient suffered attacks of pain in the right hypochondrium, radiating to the back and right shoulders accompanied by nausea, vomiting and chills, usually at midnight. The attack preceding the present illness was the severest. There was transient jaundice and acholic stools. Several weeks prior to admission the patient had a biliary colic associated with the vomiting of a small amount of dark blood.

The physical examination disclosed nothing significant. There was no icterus. Laboratory findings showed an icterus index of 10, bilirubinemia 0.3 mg. per 100 c.c. The Van den Bergh reaction was faintly delayed positive. The cholesterol content of the blood was 220 mg. per 100 c.c., the ester fraction 75 mg. The leucocytes were counted 11,100 per cubic millimeter.

An edematous hemorrhagic gall bladder containing one large walnut shaped stone was removed at operation. The patient ran a febrile course, 100 to 101 degrees Fahrenheit for 17 days following operation. She was finally discharged, relieved of her symptoms.

The gall bladder was assumed to be the source of bleeding. The history of hematemesis several weeks prior, indicated that the hemorrhagic process was probably dated then. The edematous state of the gall bladder interfered with the patency of the cystic duct preventing continued passage of blood into the bowel.

Case No. 4. Chronic Cholecystitis, Cholelithiasis, Hematemesis, Acute Pancreatitis, Transient Jaundice, Adiposity.

I. M. A female, aged 46, suffered post-prandial distention, belching and occasionally vomiting directly after meals. About eleven days before admission to the hospital she began to complain of vague generalized aches and three days later had a sudden onset of severe cramp-like periumbilical pains. She vomited some coffee ground material. The symptoms lasted for several hours. Vomiting recurred. Soreness about the navel persisted. The morning of admission she had a recurrence of pain and again vomited coffee ground material.

The physical examination indicated an extreme degree of adiposity. There was some tenderness in the periumbilical region. The icterus was slight. The blood indicated showed only a latent jaundice. The urea content of the blood was normal, the glucose elevated to 150 mg. per 100 c.c. The cholesterol was elevated to 300 mg. per 100 c.c. and the ester fraction was markedly depressed to 45 mg. In the next six days the total and ester fraction returned to normal. The blood amylase was definitely elevated to 16.4 units on admission with return to normal five and seven days after admission. Acetone was present in the urine, and disappeared on administration of fluids. The Graham test failed to visualize the gall bladder on

three repeated attempts. The barium meal indicated no abnormal findings. The patient ran a febrile course despite the cessation of vomiting and abdominal pain. This was attributed to a subsiding pancreatitis. Owing to the extreme adiposity, the favorable course of events and the reluctance of the patient to undergo immediate exploration, surgical intervention was deferred until considerable weight reduction was achieved. For six months symptoms did not recur. Thereafter the patient escaped observation. The cause of the hematemesis was not demonstrated.

Case No. 5. Acute Gangrenous Cholecystitis with Sloughing, Chronic Cholecystitis, Cholelithiasis, Pericholecystic Abscess, Thrombosis and Erosion of the Cystic Artery, Hematemesis, Post-Operative Bleeding.

T. N. A female, aged 45 years, had suffered two attacks of severe pressing epigastric pain radiating to the right hypochondrium 15 years previously with nausea and vomiting and once accompanied by dark urine and jaundice. She was in good health up to two days before admission to the hospital when she developed excruciating epigastric and hypochondriac pain radiating to the back and right shoulder, accompanied by nausea and vomiting and a constant dull ache in the right hypochondrium. The vomitus contained a large amount of blood, the urine was dark, the stools tarry. Icterus and pruritus were marked on admission. A somewhat tender mass was palpable in the right hypochondriac region. Due to the fact that the patient was a poor operative risk the operation was necessarily delayed for 18 days despite fever and chills. Then a huge abscess cavity containing gall stones was found in the region of the gall bladder. Aspiration of pus was followed by brisk bleeding. Transfusion was promptly performed. Hemorrhages again occurred on the 9th and 11th days after operation. Again transfusions were performed. Death occurred on the 12th day with hyperpyrexia. Following the operation the bilirubinemia which had been 3 mg. per 100 c.c. dropped to 0.5 mg.

Necropsy disclosed an acute gangrenous cholecystitis with sloughing, and fat necrosis of the pancreas. The cystic artery was thrombosed and eroded. An acute serosanguinous peritonitis was also present.

The hematemesis early in the history probably originated from the gangrenous gall bladder or eroded cystic artery which subsequently thrombosed. The post-operative bleeding occurred from the same eroded artery.

Case No. 6. Chronic and Acute Cholecystitis, Cholecysto-Duodenal Fistula, Gall Stone Ileus, Melena.

C. L. A female, aged 47 years, experienced digestive disturbances, gaseous eructations, epigastric distress, abdominal distention, and occasional vomiting over a period of seven years. Seven years before, she had an episode of sharp pain in the right hypochondrium radiating to her shoulders and back with nausea, vomiting, fever and definite jaundice. Tarry stools occurred with certainty at this time. Pain and vomiting lasted for a fortnight, jaundice for a month.

During the seven months preceding admission she had frequently noted tarry stools and had lost both weight and strength.

The examination exhibited diffuse abdominal distention, and fecal vomitus. An abdominal mass was not palpable. Enterotomy was performed and a gall stone removed. The distention and vomiting were promptly relieved. However, restlessness and hyperpyrexia set in wtih fatal outcome.

Necropsy demonstrated the status after ileostomy for impacted gall stone ileus. A cholecysto-duodenal fistula was present. A small shrunken gall bladder with ulcerated interior and containing a blood clot was found. The liver was ulcerated and perforated in the region of the gall bladder bed.

The early history of an acute episode with tarry stools seven years previously fixes the probable date of establishment of the cholecysto-duodenal fistula. The recent bleeding arose from the ulcerated areas in the gall bladder and liver secondary to the recent acute inflammatory flare-up.

CLASSIFICATION

Naunyn (1892) classified the types of bleeding associated with gall stones:

1. Cholemic, with hemorrhage into the gastro-intestinal tract.
2. Portal vein thrombosis complicating cholelithiasis with bleeding into the bowel.
3. Perforation of a gall stone into the lumen of the bowel or into the liver with gastro-intestinal bleeding.
4. Hemorrhage from the bile passages into the bowel.

Budinger (1925) developed a more comprehensive classification:

I. Hemorrhages, Non-Dyscrasic in Nature.
   - A. Spontaneous Bleeding from Bile Passages and Adjoining Vessels.
     1. Spontaneous massive bleeding from known blood vessel.
     2. Spontaneous massive bleeding from unknown blood vessel.
     3. Spontaneous bleeding from ulcerated areas and superficial lesions.
   - B. Hemorrhage from Neighboring Structures (including liver) with Drainage of Blood through Bile Passages.
     1. From aneurysms.
     2. From the liver.
   - C. Operative Hemorrhages.
     1. From known blood vessel.
     2. From unknown blood vessel.
     3. From liver bed or operative field.

II. Cholemic-Dyscrasic Bleeding.
   Multiple hemorrhages in various organs including gastro-intestinal tract.

The Author has modified this classification:

1. Hemorrhages of Local Origin.
   - A. Portal in Origin.
     1. Secondary to liver disease, i.e. portal hypertension. Ruptured varix.
     2. Secondary to portal vein disease, i.e. thrombosis, cavernomatous transformation.
   - B. Hepatic in Origin.
     1. Hepatic congestion and inflammation, i.e. acute and subacute liver atrophy.
     2. Traumatic.
   - C. Origin in Biliary Tract.
     1. Vascular. Rupture of aneurysm. Erosion of blood vessel by gall stone decubitus ulcer, or inflammation and ulceration of gall bladder wall. Post-operative bleeding vessel. Perforation of gall bladder into bowel, eroding vessel.
     2. Diffuse inflammatory disease of gall bladder with hemorrhage into lumen and no demonstrable bleeding vessel. Infarction and hematoma of gall bladder wall. Hemorrhagic cholecystitis.
     3. Neoplastic disease of passages with ulceration.

D. Gastro-intestinal in Origin.
   1. Ulcer complicating obstructive jaundice.
   2. Jaundice complicating peptic ulcer (Catarrhal Jaundice). Cicatricial contraction of the papilla of Vater.

II. Hemorrhages of Systemic Origin.
   Associated with hepatic insufficiency and hemorrhagic tendency. Gastro-intestinal erosions, toxic in origin.

CITATIONS FROM THE LITERATURE

I. Hemorrhage from the Gall Bladder.

A. Bleeding Source Demonstrable.

Schmidt (1893) described a patient with four massive hemorrhages in the course of five weeks, one accompanied by icterus. Despite gastric symptoms the presence of gall stones was suspected. Necropsy demonstrated a gall bladder with three areas of perforation into the duodenum each obturated by a gall stone. These were not bleeding. A false aneurysmal thrombotic mass was found between the neck of the gall bladder and the hepatic duct with pressure on the hepatic artery. The cystic duct was intact. Blood passed freely from the cystic into common hepatic duct and then into the bowel. It was difficult to determine whether a stone had ulcerated through the common duct and the artery with secondary aneurysmal formation or whether a marked cholangitis had weakened the vessel wall. Chiari's case, similarly, bled from the cystic artery. The gall bladder was involved in an inflammatory process.

Schnyder (1915) reported a case of fatal bleeding into the peritoneal cavity from a perforated gall bladder. Ulcerations had produced bleeding into the gall bladder and thrombosis of a blood vessel in its wall. Some blood had escaped into the common duct but recent bleeding into this duct had been prevented by blood clot formation and occlusion of the cystic duct. Ulceration had extended through the gall bladder wall, eroded a vessel and caused a fatal hemorrhage. No gall stones were present.

Lobstein noted a case with recovery following perforation of the gall bladder with bleeding into the gall bladder and the peritoneal cavity. The bladder and stones were removed. Gjellerup, Huguenin and Leaved have recorded similar instances.

Esau (1925) described a patient with abdominal colic followed by occult blood in the stool for 14 days. Local tenderness in the gall bladder region persisted. Peptic ulcer was diagnosed because of the bleeding, although the possibility of diseased gall bladder was also entertained. There was no icterus. No X-ray examination was made. The stomach and duodenum were found to be normal at the operation. 17 days after blood was first observed in the stool. A thickened gall bladder contained several stones. One was found in the cystic duct. The common bile duct was free. The entire inner aspect of the gall bladder wall was infarcted. The patient made a complete recovery.

Heusser's case (1925) recovered following cholecystectomy. Cystic duct occlusion prevented bleeding into the bowel. The gall bladder was filled with blood clots. its wall ulcerated and infarcted. The mucosa was completely denuded. Hemorrhage occurred by seepage and not by vessel erosion. Carnioley (1927) recorded a case of hemorrhagic cholecystitis with cystic duct occlusion and without intestinal bleeding.

Junghanns (1930) recorded a necropsy finding of decubitus gall stone ulcer eroding a vessel in the neck of the gall bladder. The cystic duct was patent. Death was caused by hemorrhage. Kehr has also referred to erosion of the portal vein and hepatic artery by common duct stone with profuse bleeding into the common duct. Naunyn recalled two cases with hematemesis caused by pyelthrombophlebitis secondary to pressure of a stone in the cystic duct.

Reports of gastro-intestinal bleeding in the course of the formation of cholecystoduodenal fistulae by passage of gall stones into the bowel are too common to enumerate in this brief account.

B. Bleeding Source Not Demonstrable.

Vysin (1923) reported a patient with attacks of colic and blood in the stools. Peptic ulcer was diagnosed. Ulcer was not demonstrable at laparotomy. The gall bladder was chronically thickened and shrunken and contained no stones. A bleeding source could not be found. Healing of an ulcer in the lapse of six weeks before operation was considered possible. Bleeding associated with gall bladder disease was apparently unfamiliar to the author.

Budinger (1925) recorded four cases. The first patient bled severely from a decubitus ulcer of the common duct. There was recent icterus. A large amount of blood was lost through the stomach and bowel. The gall bladder was full of pus, stones, and blood. The common bile duct was ulcerated by a stone, dilated and filled with pus and blood. Following cholecystectomy the symptoms vanished. The second case was diagnosed as gastric ulcer by X-ray. Symptoms suggested ulcer but accompanied by slight icterus existed for two months. The patient had vomited a large amount of blood before admission to the hospital. Following cholecystectomy, periodic bleeding took place from the wound and the bowel. The gall bladder wall was thickened, infected and its mucosa ulcerated. A stone was found in the cystic duct. Blood was present in the lumen of the gall bladder. A recent abscess was found. The gall bladder was adherent to the abdominal wall and the jejunum. No ulcers could be found in the intestinal tract. Fatal hemorrhage occurred from the hepatic artery. The source of early bleeding in this case was not demonstrated, unless it be assumed that the cystic duct occlusion occurred afterwards. The third case was also suspected of suffering from duodenal ulcer for one year. Attacks of acute pain occurred. The stools were often tarry. Lately the symptoms of gall bladder inflammation came to the foreground. Fever, tarry stools and jaundice developed. The X-ray indicated the presence of periduodenal adhesions. An abscess was found under the liver border. The gall bladder was filled with pus and blood, its mucosa gangrenous. The cystic duct though involved, was patent. Stones were not present. The main ducts were not involved and contained clean bile. Recovery followed cholecystectomy. In a fourth case, with gall stones and two bouts of jaundice, the patient again developed icterus. A thickened distended gall bladder containing about 100 tiny stones and blood was found at operation. A small stone occluded the cystic duct. A bleeding source was not demonstrable. Blood was not demonstrable in the stool after operation. If the cystic duct occlusion is relieved, blood in the gall bladder may reach the intestinal tract sub-

sequently. This event appears then not to be related to any immediate clinical episode.

Frick and Irland (1923) noted a case with profuse hematemesis and tarry stools at the ages of 18, 20 and 36 and slight jaundice several times. At operation a distended gall bladder containing one large mulberry stone was removed. A bleeding source was not demonstrable. X-ray examination of the bowel had been negative. The stomach and duodenum was also explored at laparotomy.

DeCourcy (1928) described three cases in this category. They suffered from gall stones. They suffered severe hematemesis one to five months before laparotomy. One had three attacks of severe hematemesis in the two years prior to operation. In two cases the stomach was incised and searched for ulcer. The gall bladders were removed in the three cases. Bleeding never recurred thereafter. DeCourcy attributed the bleeding to marked hepatitis.

Polichetti (1930) described a patient with a history of a profuse hematemesis five months previously and continuous indigestion despite ulcer therapy. A bladder containing 82 gall stones was removed. The stomach and duodenum were normal. Bleeding did not recur. Chronic intermittent intestinal bleeding was cured in a second patient with identical findings in the gall bladder. The stomach and bowel also showed no source of bleeding. Bleeding did not recur following operation.

White and Jankelson (1931) recounted six cases. The first patient had suffered three intestinal hemorrhages with gross blood in the stools in three years. Barium meals on three occasions revealed a slight irregularity on the lesser curvature side of the duodenum. This was interpreted as due to active or healed ulcer, adhesions, or gall bladder pressure. A thorough exploration was made of the interior of the stomach. No adhesions were present. The small intestine and colon were normal. A slightly inflamed gall bladder containing several stones was removed. There was no recurrence of bleeding for five years after operation, the period of observation. A second case with symptoms typical of gall stones developed hematemesis and melena. Barium meal two months later, indicated no ulcer. Gall stones were demonstrable by X-ray. Operation was not performed. A third patient gave a history of recurrent slight jaundice over a period of ten years. The present attack of colic lasted 24 hours. The patient then vomited blood and coffee ground material. Jaundice set in and the pain subsided. A pathological gall bladder without stones was removed. Jaundice recurred after freedom from symptoms for three years. A barium meal revealed no abnormality. A fourth patient developed colic and hematemesis following a cholecystostomy two years previously. A stone was now found in the cystic duct. No lesions were demonstrable in the stomach or duodenum. Bleeding did not recur following cholecystectomy over an observed period of five and one-half years. A fifth patient with a long standing history of gall stones developed a profuse hematemesis, tarry stools, and mild icterus. The patient died cholemic. There was no necropsy. A sixth subject with long standing symptoms of gall stones also developed hematemesis. A week later barium meal and X-ray of the gall bladder proved negative. Two stones were found in the gall bladder which was removed. The ducts were explored with negative findings.

Bleeding from Known Blood Vessel Without Gall Bladder Disease.

A. Aneurysm of the hepatic artery.

Aneurysm of the hepatic artery has been noted by Stokes, Lebert, Quincke, Borchers, Chiari. Schmidt (1893) reported a case associated with gall stones. Trauma or infection were incriminated. Kading (1919) reviewed the matter, referred to a case, and presented a case report. Hematemesis occurred in both cases. Duodenal ulcer was suspected but not found at operation in one case. It was considered a late result of some previous trauma. In the second case, the liver was injured by a wound and hemothorax was present. In both instances the aneurysm had ruptured into the bile passages. Kading reviewed four intrahepatic and 42 extrahepatic aneurysms of the hepatic artery. Perforation occurred into the gall bladder three times, into the cystic duct three times and into the common bile duct once. Friedman (1921) reported a case from this hospital, with jaundice, and melena seven years following cholecystectomy. Carcinoma of the hepatic ducts was suspected at laparotomy. At necropsy the source of bleeding was found to be an aneurysm of the hepatic artery which had ruptured into the biliary passages.

B. Erosion of the Cystic Artery.

Jaffée reported a fatal hemorrhage from cystic artery erosion by a peptic ulcer adherent to the liver and the lower edge of the liver. Bleeding following operations for gangrenous gall bladder are often caused by erosion of the cystic artery.

Bleeding from the Liver Parenchyma Into Bile Passages.

Quincke has referred to hemorrhage from the liver secondary to infarction and embolization. Rolleston described a case of acute yellow atrophy with intestinal bleeding the predominant symptom from the outset. Strauss (1929) reported a patient with traumatic subphrenic hematoma bleeding into the bile passages as well as intraperitoneally. Roessle demonstrated a fistulous tract from the hematoma into the bile passages postmortem.

Chronic Portal Vein Disease.

Fleischhauer (1932) and Scheidegger (1933) have recently reviewed the literature on cavernomatous transformation of the portal vein. Klempeper (1928) has reported a case in the American literature.

Occult Bleeding.

Eusterman (1913) reported occult blood in the stools of 20 per cent of patients with chronic gall bladder disease and in the gastric analyses of 43 per cent. Kehr maintained that occult blood occurred more often in the stools of patients with cholecystoduodenal fistula. Peiper (1921) found occult blood in the stool of 2 of 10 cases of cholecystitis. Wohlgemuth (1928) reported a patient with gall stones and hematomas of the gall bladder wall and occult blood in the stool. The blood disappeared following removal of the gall bladder. Statistics on the incidence of occult blood in the stool of patients with gall bladder disease are not complete since most cases are admitted to surgical wards

directly and are promptly operated upon without adequate routine study.

ETIOLOGICAL CONSIDERATIONS

Gastro-intestinal hemorrhages which can be traced to a ruptured aneurysm of the hepatic or cystic artery or varix, or a vessel eroded by a decubitus ulcer or an ulcerating lesion in the gall bladder require no comment. The same is true of bleeding based on a hemorrhagic tendency due to jaundice, or malignant disease of the biliary tract.

Several hypotheses have been advanced to explain the occurrence of bleeding in gall bladder disease where a bleeding point is not demonstrable. It has been claimed that venous thrombosis may cause hemorrhage, that gastric ulcers may be embolic in origin, that toxins in the blood from chronic infection in the gall bladder may cause bleeding from the stomach and upper bowel as it does in essential hematuria or epistaxis, that hepatitis may be the underlying factor. The failure of recurrence of bleeding following removal of the gall bladder points to the gall bladder itself. The effects of vomiting and retching cannot be ruled out. However, cases have occurred with no retching. Violent vomiting in other conditions is not attended by massive hemorrhages from the bowel. In some cases the vomiting is probably induced by the presence of blood in the stomach.

Bleeding into the gall bladder may occur by seepage in a diffuse phlegmonous or hemorrhagic process. Infarction of the entire wall may occur. Bleeding into the bowel occurs if the cystic dust is patent.

Bleeding attending the formation of a cholecystoduodenal fistula may be a minor incident in the history, may even be entirely unnoticed.

The symptomatology if cavernomatous transformation of the portal vein may simulate cirrhosis of the liver or peptic ulcer. Jaundice may supervene.

Jaundice may complicate duodenal ulcer. The causes may be intercurrent catarrhal jaundice or mechanical cicatricial closure of the papilla of Vater. Obstructive jaundice may become associated with ulceration of the upper bowel.

DIAGNOSTIC FEATURES

In the presence of jaundice differentiation must be made between bleeding due to a general bleeding tendency or a local cause. Without jaundice, the cause is usually a local one. It is important to remember that gall stones may be accompanied by a massive hemorrhage. Though the bleeding source may not be demonstrable, removal of the stone-containing gall bladder promptly relieves the bleeding, as a symptom. This also rules against the probability of a missed peptic ulcer.

Parenchymal liver degeneration may be associated with frank bleeding into the duodenum. Blood was obtained by transduodenal drainage in such a case. Malignant disease of the biliary passages may thus be simulated and laparotomy performed in a case of subacute yellow atrophy.

Occult bleeding may occur in gall bladder and liver disease, though the presence of blood in the stool usually favors the diagnosis of peptic ulcer or malignant disease.

The incidence of gross bleeding in one to five per cent of our patients with gall bladder disease, in a carefully observed material confirms the estimates of other authors.

COMMENT

The massive hemorrhages occurring in individuals suffering from gall stones, without duodenal ulcer demonstrable by X-ray or laparotomy are remarkable. In some instances a history of previous hematemesis or melena may be obtained yet no cholecystoduodenal fistula can be demonstrated. Laparotomy performed soon after a hemorrhage may reveal no ulceration due to passage of a stone. It is conceivable that a superficial gastric mucosal erosion may escape the most careful search. Vomiting or a toxic factor may be responsible. Appendicitis or peritonitis has been known to be complicated by massive hemorrhage on the basis of gastric erosion, toxic in origin.

SUMMARY

Local types of gastro-intestinal bleeding associated with disease of the liver and biliary tract have been distinguished from the systemic.

Hematemesis and melena may occur in conditions other than peptic ulcer, ruptured oesophageal varix or ulcerating malignant disease of the biliary tract.

Frank hemorrhage into the intestinal tract may occur in degenerative lesions of the liver parenchyma (liver atrophy), in aneurysm of the hepatic artery, and in hemorrhagic disease of the gall bladder if the cystic duct remains patent. Bleeding into the upper bowel may occur in gall stones without jaundice and without a demonstrable bleeding point. This bleeding does not recur following cholecystectomy.

Occult bleeding may occur in disease of the liver parenchyma as well as in non-malignant disease of the biliary tract.

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ABSTRACTS

CLINICAL MEDICINE

GOLDMAN, JOEL, AND COHEN, ABRAHAM.

Abdominal Distention in Lobar Pneumonia. Ann. Int. Med., IX, 1222, March, 1936.

In discussing the origin of gases in the intestinal tract the authors make clear that they are interested in those gases which are not readily absorbed, such as hydrogen, nitrogen and methane, *though admitting that other gases* may accumulate in the intestinal tract in a rate of formation in excess of their rate of absorption. In discussing the origin of intestinal gas, Cutting is quoted, in which he held that the origins were (1) composition of food stuffs, (2) diffusion of gas from the blood stream, (3) swallowed atmospheric air. He went on to discuss their production by stating that one source was from the action of bacteria on sugars in the lower portion of the small intestine; (2) the action of bacteria on cellulose residue remaining undigested; that free hydrogen occurred in the blood stream under pressure of 4/5 of an atmosphere, *while oxygen and carbon dioxide occurred* in chemical combinations only. The nitrogen is left free to leave the blood stream to replace other gases in the intestine when pressure relationships are favorable, whereas in order for oxygen or carbon dioxide to leave the blood stream there must not only pressure relationships be disturbed, but also must conditions be favorable for the liberation of these gases from their chemical combination. Alvarez is quoted as stating that little or no trouble was experienced from flatulence in a series of patients at the Rochester Clinic suffering from pneumonia when treated in a chamber containing 50 per cent of oxygen, because in such an atmosphere more of the nitrogen in the bowel could diffuse out. The consensus of opinion of authors consulted in the preparation of the paper appeared to warrant the conclusion that putrefactive and fermentative changes in the intestines were of minor importance as compared to disturbances in the diffusion of gases and that an additional embarrassment of the *circulation resulted from* chemical interference with the splanchnic circulation or perhaps also from compression of the heart through the *diaphragm; that in abdominal* distention it was thought that gaseous distention depended chiefly upon alterations in the interchange of gases between the gastro-intestinal tract and the blood. Thus the normal equilibrium of these gases could be upset by disturbances in the toxicity and motility of the gastro-intestinal musculature or by interference with the local fixation. In *pneumonia* possibly the diminished capacity of the lung may thus be in part responsible for the distention commonly associated with that disease.

A discussion of the drugs that have been recommended to be used to combat distention of this nature follows, with the conclusion that none of them was satisfactory in all cases. Impressed by the report in 1933 of Paine, Carlson and Wangensteen, describing a form of continuous lavage of the duodenum by means of a nasal tube to relieve postoperative distention, nausea and vomiting, the authors introduced a modification of this apparatus to be used in the management of abdominal distention in *lobar pneumonia and other conditions* producing distention. The modification of the continuous lavage of the duodenum consisted in its application to rectal suction siphonage. The only difference in the apparatus used by the authors and that described by Paine and his associates was the substitution of a soft rubber rectal tube for the Levine duodenal tube. The technique of its use consisted in giving a cleansing soapsuds enema before the apparatus was set in action and an attempt to keep the stools in a liquid state to prevent block of the tubes. This latter desideratum is obtained by the use of saturated magnesium sulphate solution. The use of the apparatus was continued as long as necessary to reduce the distention and discontinued so soon as the distention was relieved, and was repeated whenever necessary. The only untoward effect was tenesmus. The authors treated 100 cases and report control of distention in less than 24 hours in most of the cases, only 18 per cent requiring a longer period for control. Rectal irritation occurred in 13 per cent; in 34 per cent the distention was controlled notwithstanding a fatal termination. It was concluded the procedure gave added rest to the patients, that the need of bed-pan disturbance was reduced, the nursing problem was simplified, that it could be carried out in the home as well as in the hospital, that incontinence was infrequent and that it is safe, inexpensive and effective.

Virgil E. Simpson, Louisville.

RATTNER, H.

Stomatitis Due to Sensitization to Dental Plates. J. A. M. A., Vol. 106, pp. 2230-2232, June 27, 1936.

Stomatitis due to sensitization to material in dental plates is a condition not generally recognized by dentists or physicians. The author presents three cases who developed stomatitis after changing their dental plates or having their old ones repaired with new materials.

The severest of the cases was characterized by burning tongue, excessive salivation, soreness of the mucous membranes of the entire oral cavity, nausea, eructations and a thick discharge from the mouth occurring towards the end of the day. Examination revealed a markedly inflamed mucous membrane with serous exudation. The other cases were of less severity. In two of the cases there was a positive patch test where the plate was applied to the arm.

The composition of the material from which dental plates are made is a trade secret, but enough is known about them to indicate that they contain substances which may be irritating to susceptible cases.

Francis D. Murphy, Milwaukee.

MENTZER, STANLEY H.

Obstructive Cholecystitis. S. G. O., Vol. 62, No. 5, May, 1936.

The author discusses Obstructive Cholecystitis with particular reference to acute obstructive cholecystitis and its sequelae. He discusses the progressive steps in the pathology of acute obstructive cholecystitis to empyema which is the eventual outcome. In this connection he points out that the mortality in the treatment of acute cholecystitis will be decreased if the obstructive lesions are differentiated, clinically, from the non obstructive. Dr. Mentzer

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is of the opinion that acute cholecystitis that cannot be differentiated clinically, should be operated upon within 6 to 48 hours after the patient enters the hospital.

In dealing with nomenclature applied to gall bladder pathology, the author suggests that the term "Acute Obstructive Cholecystitis" be applied to the suddenly obstructed and acutely inflamed gall bladder which is still filled with bile. The adjectives fibrinous, phlegmonous, and gangrenous may be added to define the pathological condition further, if desired. The terms "hydrops" and "empyema" are used to designate the obstructed gall bladders, filled with mucus or pus. Acute and subacute exacerbations of these are indicated by these adjectives.

The progression of the pathological condition from acute obstructive cholecystitis to hydrops and finally to empyema is dependent upon the time element and upon the presence of old or recent infection. If these could be determined clinically, the type of obstructive disease might be anticipated. It is usually impossible, however, to determine which colic, if any, resulted in complete obstruction and it is even more difficult to decide when the onset of fresh infection has occurred. Under these circumstances, it is not surprising that so few correct pre-operative diagnoses of the exact stage of the process are made.

Dr. Mentzer thinks it is unfortunate that surgeons too often content themselves with a diagnosis of acute cholecystitis and then treat the patient conservatively to await subsidence of the acute infection. In his own experience the mortality with excessive conservatism was 56%. This has been reduced by more accurate diagnoses and by earlier surgical intervention to 15% in obstructive cholecystitis. Their mortality with perforated gall bladders with delayed operation was 55% in 1932 and with early operation 41%. At present it is 44 and 11% respectively.

He states that if the acute cholecystitis is so marked that abdominal rigidity prevents the palpation of a mass and therefore prevents us from differentiating the obstructed from the non-obstructed forms of acute cholecystitis, as well as inhibiting the differential diagnosis of the three types of obstructive cholecystitis, then we should observe the patient for 6 to 48 hours before instituting surgical therapy. If fever, leucocytosis, tenderness, and rigidity have not definitely subsided in this period, surgical exploration should be done for we know we are dealing with an advanced, acutely inflamed gall bladder. Under this policy, the author states, their mortality has decreased.

The author reviews 149 consecutive gall bladder operations performed on the University of California service at the San Francisco Hospital in the past 6 years; 51 of these were for obstructive cholecystitis. Most of the obstructive lesions were encountered in women (72%) and the major number of the patients were in the age group 40 to 60 years. Eight per cent of the patients having hydrops, 12% of those having empyema and 30% of those having acute obstructive cholecystitis states that they had never suffered from any symptoms that might be even suggestive of previous cholecystic disease. The temperature curves were highest in the empyema cases and lowest in the hydrops. Jaundice had not been observed by any of the 10 patients who had acute obstructive cholecystitis and only 2 of the 24 who had hydrops had had any icterus. Neither of these groups had jaundice with the present illness. Of the 17 having empyema however, 6 were icteric while in the hospital.

Most of the operations performed on the 51 cases of obstructive cholecystitis were cholecystectomies but the author feels that, even at that, an unduly high percentage, 35% were cholecystostomies. The author feels that cholecystostomy is often the operation of choice, particularly in the aged, debilitated, and very ill, but when done, it should be remembered that a cholecystectomy will probably be necessary later.

Charles T: Sturgeon, Los Angeles.

MARTIN, KIRBY A.

Histidine Hydrochloride Versus Diet and Alkalis in Treatment of Peptic Ulcer. J. A. M. A., Vol. 106, p. 1468, April 25, 1936.

Histidine was first used by Weiss and Aron of Strasbourg in 1933. They based their work on experimentally produced ulcer by the Mami-Williamson technic, which was treated by the injection of histidine. Since the use of this substance began, there have been many favorable clinical reports concerning its efficacy in the treatment of peptic ulcer in human subjects. Because of these reports, a series of 41 selected patients with acute symptoms and radiologic signs of peptic ulcer were treated with the substance.

The histidine was given intramuscularly. All but three of the patients were kept ambulatory, and their diets were not changed. The immediate response to this therapy was prompt and uniform. Thirty of the patients were relieved of their symptoms at or before the conclusion of the treatment. Fourteen of these showed X-ray evidence of a healed ulcer and twelve showed a crater still present. Eleven showed no improvement.

The patients were observed for from six months to one year. At present, thirteen are symptom free and twenty-six have had relapses. Of the twelve rendered symptom free, but in whom a crater persisted, only three have remained symptom free, whereas of the fourteen rendered symptom free in whom no crater could be demonstrated, ten have remained so.

A second, or control group of 40 similar cases was selected and put upon the diet-alkali regime. At the end of four weeks, a period corresponding to the histidine treatment, thirty-one were symptom free. They were observed for one year. Sixteen have remained symptom free and twenty-six had relapses.

The symptomatic and radiologic response of the patient in the histidine series was not quite as good as that in the diet-alkali regimen series, in either the initial or the sustained effects.

The clinical improvement following histidine therapy appears to be symptomatic and transient. Histidine merely alters the rhythm of the course of peptic ulcer. It showed no constant effect on the secretion of hydrochloric acid in this series. The indications for histidine hydrochloride therapy are limited and results are not as good as previously thought.

Francis D. Murphy, Milwaukee.

MEYER, K. A., AND ROSE, P. A.

Regional Enteritis (non-specific). S. G. O., Vol. 62, No. 6, pp. 977-988, June, 1936.

The authors report a series of eight (8) cases of regional enteritis seen during the last two years. The path-



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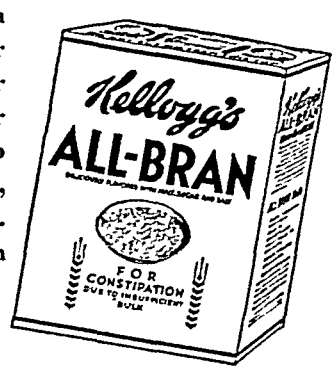
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ological process may be divided into three stages: (1) acute regional enteritis. (2) chronic hypertrophic enteritis with stenosis of the lumen, and (3) chronic enteritis complicated by external or internal intestinal fistula. The process is usually sharply demarcated at the ileocecal valve and may or may not end abruptly at a point proximal to the ileocecal valve. A thickened edematous mesentery may indicate perforation between its leaves and may be an indication as to treatment to be followed. Abscesses in the mesentery may rupture into other loops of bowel or into the colon to establish a fistula.

The symptoms of regional enteritis may be divided into four groups according to Crobu: (1) segus of an "acute surgical abdomen," (2) symptoms of ulcerative colitis, (3) symptoms of chronic obstruction of the small intestine, and (4) persistent intestinal fistula following drainage of an abdominal abscess. The symptoms in one-half of the author's cases simulated acute appendicitis. Recurring colic-like intermittent pain of acute intestinal obstruction was present in three of the cases. No case had a history of diarrhea. A moderate leukocytosis was present. Roentgen ray examination of the gastro-intestinal tract is entirely negative, or shows a filling defect in the terminal ileum. In the advanced cases the string sign of Kantor may be seen.

The treatment of acute regional enteritis depends on the stage of the process. If the mesentery is not involved and there is no obstruction, conservative treatment may be chanced. If the mesentery is thickened and edematous, or there is a fistula present, wide resection of the diseased parts is necessary.

Eight cases are reported in detail. Fourteen figures accompany the article.

Nelson M. Percy, Chicago.

ALVAREZ, W. C.

Severe Gastric Hemorrhage Produced by Violent Abdominal Massage. J. A. M. A., Vol. 107, p. 124, July 11, 1936.

Severe exertion involving the abdominal muscles may produce a gastric hemorrhage in patients with peptic ulcers. The case here reported is that of a man who had had symptoms of a duodenal ulcer since eleven years of age. He placed himself in the hands of an irregular practitioner who placed a large electrode on the lower abdomen and sent through him a rhythmically interrupted current which caused severe contraction of the abdominal muscles. He became severely distressed and vomited up large quantities of blood. He was almost completely exsanguinated, and had to be transfused several times. From this it is obvious that abdominal massage, or excessive use of the abdominal muscles is contraindicated in peptic ulcer.

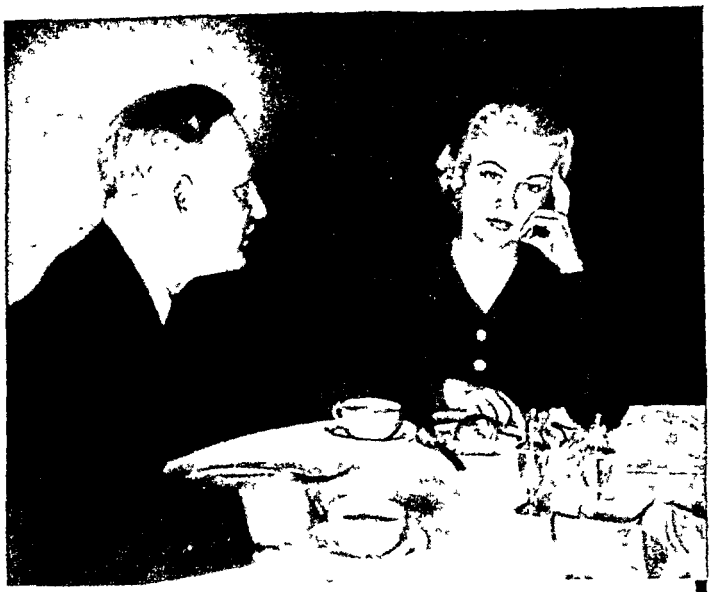
Francis D. Murphy, Milwaukee.

EXPERIMENTAL PHYSIOLOGY

BOLLMAN, J. L., AND MANN, F. C.

The Influence of the Liver in the Formation and Destruction of Bile Salts. Amer. Jour. Phys., 116, No. 1, 214-224, June, 1936.

The authors using the method of Gregory and Pascoe studied bile salts in bile, urine, and blood under various conditions. They find that in the normal dog bile salts are not detectable in the blood and urine; on intravenous injection of glycocholates or taurocholates, only a small amount is recovered in the urine and feces, while they disappear from the blood quite rapidly. With complete hepatectomy, bile salts are not detectable in the blood and urine; and injected salts are practically quantitatively recovered in the urine within twelve hours. With complete biliary obstruction bile salts increase in the blood and urine; the bile salts in the blood remain markedly increased for about two weeks and then drop to a low, but detectable level at which they remain, urinary output of bile salts



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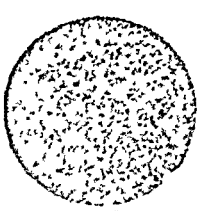
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remains fairly constant throughout the course.

Intravenous injection of bile salts in animals with complete obstruction, results in increased urinary excretion, but recovery is about 60% as compared to 95-100% in hepatectomized dogs. Urinary output of bile salts in animals with complete obstruction is one-half to one-third the amount excreted by animals with biliary fistulae. Hepatotoxins markedly diminished the bile salt level in blood and urine in these animals as well as in the bile of bile-fistula dogs. The authors conclude that the data is evidence of hepatic production and also destruction of bile salts, and that hepatotoxins alter the process of formation.

I. S. Cherry, Chicago.

BETTMAN, RALPH BOERNE, AND TANNENBAUM, WILLIAM J.

Gall Bladder Contractility After Blood Transfusion. J. A. M. A., Vol. 106, pp. 1376, April 18, 1936.

Ivy was the first to isolate cholecystokinin from the mucosa of dogs and demonstrated that the contractility is initiated by a hormone. Sandblom apparently proved that this hormone is transmitted by the blood by showing that in fasting individuals the gall bladder contracted after receiving blood from a donor who had previously eaten a fat meal.

Bettman and Tannenbaum selected nine healthy individuals, gave them a breakfast high in fat content and withdrew blood from them in an hour and a half after the ingestion of the meal.

A patient who had a normal concentration of dye in the gall bladder and normal emptying of it, but who also had one calculus, was selected. The gall bladder dye was given in the evening, and in the morning the film showed a large distended gall bladder and good concentration. One hundred cubic centimeters of high lipoid serum was given and X-rays taken ten minutes, one-half hour, one hour and two hours later showed no emptying. After two hours the usual fat meal was given, and a film taken one hour afterward showed normal emptying.

A similar experiment was tried with the transfusion of whole blood with the same results.

The conclusion was reached that neither high lipoid content serum or whole blood transfusion from a patient who has recently had a fatty meal will cause contraction of the gall bladder.

Francis D. Murphy, Milwaukee.

NUTRITION

MILLER, D. K., AND RHODES, C. P.

The Effect of Liver Extract on the Small Intestine of Patients with Sprue. Am. Jour. of the Med. Sci., p. 453, April, 1936.

A clinical study of a group of patients with sprue was made and it was observed that flatulence, intestinal discomfort, cramps and diarrhea recurred unless a sufficient amount of liver extract was given frequently. The intestinal dysfunction was independent of the anemia and larger quantities of liver were necessary for its control than for that of the anemia. This suggested a relationship between liver extract and intestinal activity.

Characteristic morphological alterations of the small intestine of patients with sprue were found by X-ray studies and consisted of: 1, a segmental distribution of barium, produced, it is inferred, by abnormal motility of portions of the small intestine; 2, a variation of contour and caliber of the intestinal segments; 3, a distorted mucosal pattern, especially of the duodenum and jejunum, but often of the ileum as well; 4, an outline of the terminal ileum which appears straighter than normal and gives the impression of a lack of pliability of the intestinal wall. The authors report a case of

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sprue exhaustively studied and followed for three years. She was gravely ill. Under large doses of liver extract intramuscularly, her profound anemia improved, there was a reticulocyte response of 42% and in 7 weeks her r.b.c. were 4,170,000 and hgb. 73%. Diarrhea, which was present before treatment was begun, was immediately checked but recurred if a longer period than two weeks elapsed between injections of liver extract. Roentgenray examinations made in the presence of diarrhea and after its cessation demonstrated that the segmental distribution of the barium throughout the small intestine and a residue of barium in the stomach for 6¾ hours with the diarrhea gave place to a smooth continuous outline of the barium throughout the small intestine and the stomach was empty in two hours.

Summary: 1. Roentgenologic evidence of abnormal form and function of the small intestine of a patient with sprue, without anemia but with diarrhea is presented.

2. A return toward normal form and function, as evidenced by roentgenologic study, as well as the disappearance of symptoms followed the injection of liver extract.

3. It is suggested that liver extract administered parenterally conditions the functional activity of the small intestine.

Allen Jones, Buffalo.

BLOTNER, HARRY.

Effect of Alcohol on Digestion by Gastric Juice, Trypsin and Pancreatin. J. A. M. A., Vol. 106, 23, June 6, 1936.

The author had previously found that alcohol prevented the digestion of insulin by gastric juice, trypsin and pancreatin, and it appeared that alcohol had either destroyed or inactivated the enzymes. Since an *in vivo* inactivation of enzymes in drunkards might help to explain their neuritis on the basis of a food deficiency state, Blotner carried his experiments further. Normal gastric juice freshly collected failed, when mixed with suitable amounts of alcohol, to digest egg white in any degree, and results were the same when commercial trypsin and pancreatin were tested in the same way. Blotner went further and tested the proteolytic activity of aspirated gastric juice from persons recovering from prolonged bouts of heavy drinking and found that the proteolytic activity of the juice was absent. He noted, however, that these samples contained no free HCl, and proceeded to add HCl to the samples but still obtained no digestion of coagulated egg-white. He concludes that "considering the chronic alcoholic patient with polyneuritis or deficiency disease, it would appear that the large quantities of liquor taken over a long period of time destroys digestive enzymes and thus prevents the proper digestion and assimilation of food." Such a conclusion is scarcely justified in the sense in which the author means it. It is not unusual to find an achlohydria in an alcoholic but there is no proof that the patients pancreatic secretion is either absent or inactivated.

Beaumont S. Cornell, Fort Wayne.

ROENTGENOLOGY

HARRIS, JOHN H.

Primary Jejunal Ulcer. Radiology, Vol. 26, No. 4, April, 1936.

A case was recently examined in the Radiological Department of the Carlisle Hospital in which there were found two perforated primary jejunal ulcers.

H. S., male, aged 48 years, was seen by his family physician in September, 1933, complaining of upper abdominal pain accompanied by vomiting of bile-stained material. There was some radiation of pain toward the right lower quadrant suggesting an appendi-

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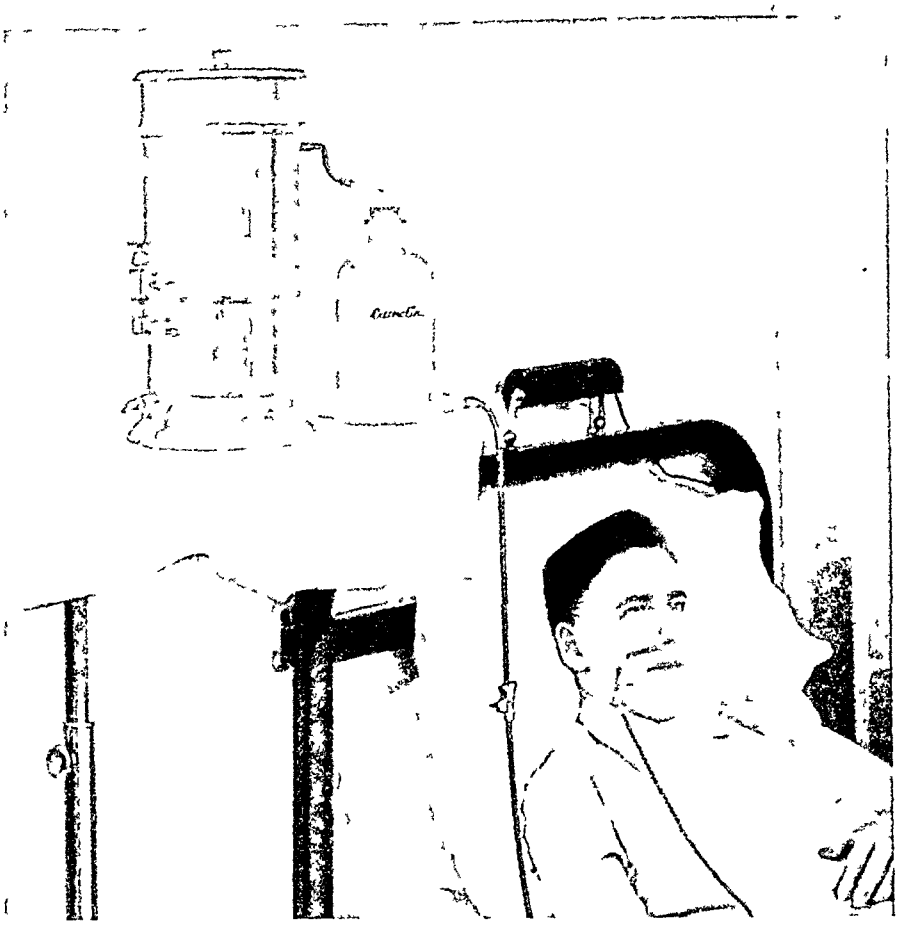
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The continuous drip method in the treatment of peptic ulcers was suggested by the desirability of constant neutralization of the excess hydrochloric acid, night and day. Excellent results, as evidenced by roentgenological examination, have been reported. • • The continuous drip treatment requires a neutralizing agent that has high combining power and that can be administered in large volumes without toxic effects, and a simple, dependable apparatus for maintaining the continuous drip. • • **THE CREAMALIN AUTOMATIC DRIP CONTROL** facilitates the technique of the drip method of administration. The solution drips into the patient's stomach, via a Levine tube, without quantitative or qualitative change, day and night. The apparatus is compact, sturdy, easy to operate, and requires a minimum of attention. • • Creamalin, a specially prepared cream of colloidal aluminum hydroxide, is especially suitable as the neutralizing agent in the continuous drip treatment. It possesses the necessary combining power, **combining with 14 volumes of tenth-normal hydrochloric acid by physical fixation in one hour.** Creamalin is miscible with water and will not cause clogging in the apparatus. A pint of Creamalin diluted with three parts of distilled water can be administered every 24 hours as a continuous drip without disturbance to the acid-base balance and without toxic effects of any kind. • • Creamalin has been administered orally with satisfactory results, but it has produced its most spectacular results by the continuous drip method, especially in refractory cases. A number of these were bleeding peptic ulcers and others were cases where surgical intervention had been contemplated. • • In one institution alone 62 cases have been treated by the Creamalin Drip and, with one exception, x-ray evidence indicated healing of the ulcerated area within seven to ten days. • • Write for further information and material for clinical trial.

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ceal attack. The attacks subsided and he was seen three months subsequently with symptoms suggesting gastric ulcer. The symptoms were controlled by ulcer regime. In January, 1934, he developed another attack of acute abdominal pain accompanied by hiccoughs. At that time the white blood count was 15,000. One week later the attack subsided. In March he was admitted to the hospital for a gastro-intestinal X-ray study. The stomach was of the cascade type and contained a large amount of residue. Numerous fluid levels were seen in the large and small bowel. At times, during the fluoroscopic examination, it seemed that an ulcer niche could be made out on the posterior wall of the stomach in the region above the incisura angularis.

Films revealed the presence of a fleck which led to the diagnosis of an ulcer on the posterior gastric wall. The appearance of the distended colon with multiple fluid levels suggested lower bowel obstruction. For this reason a barium enema was done one week following the oral meal. Again the fleck was seen in the same position as it was one week before. As no barium nor bismuth had been given the patient during the interval, it was concluded that a small gastro-colic fistula existed which permitted the ulcer niche to fill during the enema examination. Upon the basis of this diagnosis an exploratory operation was performed and no pathology was found by the surgeon. The appendix was removed and the patient made an uneventful recovery.

On November 1st, after feeling well during the interval, the patient had a recurrence of upper abdominal pain and vomiting. The fluoroscopic examination was unsatisfactory because of vomiting. The patient went into shock and died. At postmortem, the abdomen was found to be filled with straw-colored fluid. The intestines were matted together by a plastic exudate. An abscess was found in the left upper abdomen in a curve of the distal transverse colon. This abscess developed from two perforated jejunal ulcers, which were opposite each other, one on the posterior and one on the anterior wall, and were located four inches from the duodenal-jejunal junction, and there were enlarged soft lymph nodes along the mesenteric attachment.

Pathological report revealed no evidence of malignancy.

Primary ulcers in this part of the bowel are quite rare and more rarely still is the diagnosis made before operation.

D. S. Beilin, Chicago.

SURGERY OF THE LOWER COLON AND RECTUM

ARENA, JAY M.

"Pyloric Stricture Following the Ingestion of Muriatic Acid." South. Med. Jour., 29:331-333, March, 1936.

Esophageal obstruction following the ingestion of lye is a rather familiar picture. Lye, because of its greater concentration over the epithelial lining of the esophagus, does its great corrosive action there and, when diluted in the stomach, is relatively harmless. Acids, on the other hand, produce only a scorching effect on the esophageal mucosa, and then concentrate their effects in the region of the pylorus—even, at times, when taken in small amounts and low concentration. This scarring, which is usually slower in producing symptoms, may lead to rather complete obstruction. Its possibility should be realized and symptoms carefully looked for after acids are taken—otherwise these symptoms may be confused with other factors. An interesting recovery in a child of two years following a Finney pyloroplasty is reported in the article.

J. Duffy Hancock, Louisville.

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James E. Knox, Clinical Director

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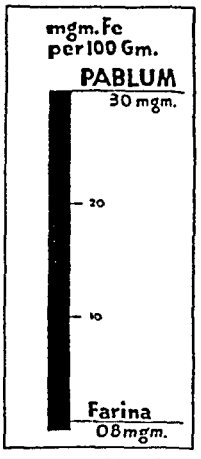
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Fig. 3. Cardiospasm with moderate dilatation of the esophagus.



Fig. 5. Perforation through the wall of the esophagus.



Fig. 4. Rehfuss tube passing through the esophagus into the stomach, with the angulated portion protruding through the wall of the esophagus.



Fig. 6. Showing perforation extending through the posterior wall of the trachea.



Fig. 3. Cardiospasm with moderate dilatation of the esophagus.



Fig 4 Rehfuss tube passing through the esophagus into the stomach, with the angulated portion protruding through the wall of the esophagus.



Fig. 5. Perforation through the wall of the esophagus.



Fig. 6. Showing perforation extending through the posterior wall of the trachea.

until gastrostomy was performed the patient lost 85 pounds (38.6 kg.); following insertion of the tube, however, he regained 25 pounds (11.3 kg.). In spite of the pronounced dysphagia, fluids would occasionally pass from the esophagus into the stomach.

Roentgenoscopic and esophagoscopic examination revealed cardiospasm (Fig. 1). Dilatation of the cardia and closure of the gastric stoma relieved the patient of his symptoms.

Case 2. A man, forty years of age, was examined August 8, 1933. In December, 1932, he had been ill with influenza for about three weeks. About the time he was able to be up he was injured in an automobile accident and suffered considerable trauma over the abdomen, associated with the vomiting of blood. A week later he vomited a large amount of blood. This was repeated three days later, and then, for two or three weeks, he noted tarry stools. By the first of April, 1933, he was able to be out of bed, but soon after this he noted a burning pain in the epigastrium associated with hiccoughs and obstruction to solid food in the lower portion of the esophagus. The pain soon disappeared but the dysphagia became more pronounced.

Examination revealed a benign stricture in the lower portion of the esophagus (Fig. 2). Dilatations were carried out and, at the end of the last treatment in December, 1935, the patient was eating normally and his general condition was excellent.

Case 3. A woman, sixty-six years of age, was well until June, 1921, when she suffered a severe injury in a railroad wreck. Several ribs were fractured, and there was considerable abdominal pain associated with the passage of blood by bowel. Following this accident the patient continued to have attacks of epigastric pain which was projected substernally to the neck and lower jaw. Two months later occasional obstruction to food at the cardia was noted.

The dysphagia very gradually became worse and at the time of her *first examination* at this Clinic, in October, 1931, a diagnosis was made of cardiospasm (Fig. 3). Dilatation of the cardia was followed by almost complete relief from dysphagia, but the attacks of pain, although not so severe or so frequent, continued until the time of the patient's last examination in April, 1936.

Case 4. A man, twenty-nine years of age, who had previously been in excellent health, was in an automobile accident April 4, 1936. He was struck in the chest by the steering wheel. Immediately following this he suffered severe substernal pain which was increased on respiration; there were cough and expectoration of bloody sputum, and the temperature rose to 102 to 104° F. Five days after the accident the patient began to have difficulty in swallowing, and any attempt at ingestion of fluids was followed by severe attacks of coughing. A Rehfuss tube had been introduced for feeding.

The patient was brought to this Clinic for *examination* two weeks after the accident and his condition on admission was quite critical. He was coughing up large amounts of foul, purulent sputum and had a continuous fever, with rapid respiration and an increased pulse rate. *Roentgenographic examination* of the thorax revealed the tube in the stomach; there was a large angulated section of the tube that apparently had passed through the esophageal wall (Fig. 4). From this finding it was concluded that perforation of the esophagus had occurred and that the tube was protruding into the mediastinum. Sudden terminal hemorrhage occurred two days after admission.

Postmortem examination revealed a longitudinal rupture, 1½ inches (3.7 cm.) long on the anterior wall of the esophagus and the posterior wall of the trachea (Figs. 5 and 6). This rupture communicated with the mediastinum and gangrenous mediastinitis was present. There was very little evidence of external injury.

A Study of the Hippuric Acid Excretion as a Test of Hepatic Function*

By

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and

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THE measurement of hepatic function is especially difficult because of the tremendous reserve capacity of the liver and because of the multiplicity and interrelation of its functions. When the change is within the limit of the physiological reserve of this organ, the determination of the amount of hepatic damage cannot be measured with any degree of accuracy by the majority of the clinical tests now in general use. Tests measuring carbohydrate metabolism or excretory function may be entirely normal even when the physiological detoxification mechanism may be markedly impaired. It is in only the most severe and advanced instances of hepatic damage that we are likely to find all functions of the liver impaired to an equal degree. The detoxification mechanism of the liver is one of the more important functions of this organ, as failure of this mechanism may produce metabolic dysfunction in other organs of the body.

In 1933, Quick (1), who studied the detoxication of noxious substances by conjugation with glycine, presented a method for testing the detoxifying function of the liver. Following the work of Bryan (2), Quick devised a clinical test in which sodium benzoate was administered orally and the amount of hippuric acid excreted in the urine during a four-hour period determined. After the work of Bunge and Schmeideberg (3), and until recently, the site of the conjugation of sodium benzoate and glycine was believed to be in the kidney. These investigators used dogs in their experiments but Quick (4) repeated their work using

*From the Lilly Laboratories for Clinical Research and the Department of Medicine, Indianapolis City Hospital.
Submitted June 6, 1936.

TABLE I

This group is composed of individuals showing no clinical evidence of liver damage (that is, no jaundice and no enlargement of the liver). In each case the Wassermann was negative

Case No.	Sex and Age	Blood N.P.N. mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment
1	M. 35	—	104	3.08	Ext.	Normal
2	M. 25	—	94	2.97	Ext.	Normal
3	M. 20	—	136	3.52	Ext.	Normal
4	M. 32	—	89	3.33	Ext.	Normal
5	M. 19	—	159	3.69	Ext.	Normal
6	M. 40	30	—	3.00	Ext.	Only diagnosis hysteria.
7	F. 50	—	90	2.93	Ext.	Laparatomy for cholelithiasis; no stones; normal gall bladder.
8	F. 30	34	—	3.00	Ppt.	Lymphosarcoma (proved by biopsy).
9	F. 23	30	—	3.20	Ppt.	Gonorrheal arthritis of right knee.

rabbits. He believed that in man, as in the rabbit, the site of the conjugation, as well as the site of the synthesis, of glycine is in the liver.

Bryan was the first investigator to report the use of sodium benzoate as a liver function test but he was primarily interested in its use as a kidney function test. Quick (1, 5) reported two series of cases of various types of liver disease which were studied by means of the hippuric acid test. Vaccaro (6) reported a series of 44 cases and Snell and Plunkett (7) reported a series of 38 cases. The results published in all of these reports indicate that this test furnishes an accurate and reliable method of testing the detoxifying function of the liver. Although Quick described

TABLE II

All of these cases were diagnosed clinically as Alcoholic Cirrhosis. There was definite enlargement of the liver with ascites in every case. All showed negative Wassermanns.

Case No.	Sex and Age	Jaundice*	Blood N.P.N. mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment*
10	F. 45	None	39.5	—	0.983	Ppt.	Large amount of fluid in abdomen.
		None	—	—	1.18	Ppt.	*4 months later; no fluid present.*
11	M. 35	10†	—	72	1.90	Ppt.	Taken at time of admission.
		None	—	—	2.70	Ppt.	4 months later—at end of period of hospitalization: markedly improved clinically.
		None	—	—	2.02	Ext.	Readmitted to hospital 16 months later; condition the same clinically as on first admission.
12	M. 53	32†	35	—	1.19	Ppt.	Advanced case of cirrhosis.
		—	—	149	1.01	Ext.	One week later; died several weeks after this test of sudden hemorrhage.
13	M. 19	None	27	—	1.28	Ext.	Very large liver with ascites.
14	M. 60	None	—	79	1.90	Ext.	Bromsulphalein test showed 30% retention in 30 minutes (A).
15	M. 72	34†	—	98	0.38	Ext.	Bromsulphalein test showed 80% retention; died following exploratory laparotomy (A).

*In this and the succeeding tables
* = icteric index.
† = serum bilirubin mg. per 100 c.c.
(A) = diagnosis confirmed by autopsy.

TABLE III

This group is composed of cases diagnosed as syphilis from history and positive serology. In each case the Wassermann was four plus at the time of examination

Case No.	Sex and Age	Jaundice	Hepatic* Enlargement	Blood N.P.N. mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment
16	M. 56	117†	+ +	33	—	2.27	Ppt.	Not on treatment.
		40†	+ +	—	—	2.59	Ppt.	2 months later; clinically greatly improved; size of the liver apparently the same.
17	M. 50	4.2‡	None	30	—	3.07	Ppt.	Chancre 3 months before jaundice; received one injection of neoarsphenamine.
18		5.2‡	+	35	—	1.94	Ppt.	Had gumma of arm; several previous attacks of jaundice following neoarsphenamine.
19	M. 44	4†	+ + + +	35	—	2.46	Ppt.	Hepatic enlargement with large amount of ascites.
20	F. 49	None	None	28.5	—	2.83	Ppt	No evidence of hepatic damage.
21	M. 50	2.4‡	+ +	36	—	2.72	Ppt.	Ascites; had had no treatment.
22	M. 55	40†	+ + + +	—	98	1.006	Ext.	Ascites; no treatment.
23	F. 32	None	+ + + +	31	—	2.13	Ext.	Ascites; no treatment; marked hepatic enlargement.
24	F. 32	32‡	None	—	100	1.18	Ext.	Jaundice during course of antiluetic treatment; chancre several years before.
25	F. 30	2.5‡	None	—	73.4	2.01	Ext.	Jaundice during course of antiluetic treatment.
26	M. 37	None	?	—	99	3.40	Ext.	Tumor mass in upper right quadrant; refused surgery.
27	M. 51	2.35‡	+ + + +	—	70	0.937	Ext.	Ascites and hepatic enlargement of long standing.
28	F. 31	None	None	—	65	2.90	Ext.	Neurosyphilis; jaundiced for one year.

*In this and in the succeeding tables + = slight, + + = definite, + + + = marked, and + + + + = extreme hepatic enlargement.

two methods, all of the other investigators used only the simple clinical method in their series of cases.

Since the rate of excretion of hippuric acid depends on the kidney function as well as on the rate of synethesis of glycine and its conjugation, it is necessary to measure kidney function in these cases. Quick suggested the determination of non-protein nitrogen as a control for kidney function because hippuric acid behaves like other nitrogenous excretory products. In some cases in our series urea clearance was substituted for non-protein nitrogen determination since it was found that this test is a more delicate control for the hippuric acid excretion.

METHODS

5.9 gm. of sodium benzoate was given orally in a half glassful of water at 8 a.m. Breakfast was limited to coffee and plain toast. Quantitative urine specimens were collected at hourly intervals for 4 hours. At first four separate determinations were made, but later the specimens were pooled and a single determination was made.

These determinations were carried out exactly as outlined by Quick (1). Although the precipitation of hippuric acid by the addition of concentrated hydrochloric acid gave good results in most cases, the second method described by Quick, in which the hippuric acid is removed from the specimen by means of the continuous ether extraction method, offers some advantages which are of great practical value. These advantages are: (1) the presence of bilirubinuria does not interfere with the test; (2) the long, tedious concentration of specimens is eliminated; (3) small amounts of hippuric acid can be determined. In addition to the technical advantages of this method, a urea clearance test can be performed with the same specimens used for hippuric acid determination because after the volume has been determined only 10 c.c. of the total specimen is used for extraction, leaving the rest of the specimen for the urea clearance test. Van Slyke's (8) method was used for the urea clearance determinations.

RESULTS

Table 1. This group of 9 cases showed *no evidence of hepatic pathology.* The first 7 cases were studied by means of the extraction method and in the other 2 cases the precipitation method was used. All of these cases gave results within the limits of normal as established by Quick (1) and the other investigators (6, 7). The extraction method gave results similar to those obtained by the precipitation method.

Case 7 is of especial interest because this case presented all the symptoms of cholecystitis although surgical exploration of the abdomen revealed no evidence of pathology. However, the excretion of hippuric acid was within normal limits.

Table 2. This table includes a group of 6 cases of *definite cirrhosis* with hepatic enlargement and ascites. None of the cases in this group showed serologic evidence of syphilis.

Two determinations were made in Cases 10 and 12 at varying intervals. Case 11, who had alcoholic cirrhosis, was studied for a period of 3 years. The first

TABLE IV

Malignancies of the stomach or other organs with metastases to the liver, all cases showing enlargement of the liver of varying degrees. The Wassermann was negative in all cases except 37

Case No.	Sex and Age	Jaundice	Hepatic Enlargement	Blood N.P.N. mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment
29	M. 48	3.9‡	++++	28.5	—	0.74	Ext.	Carcinoma of stomach (inoperable) with metastasis to the liver.
30	M. 45	20†	+++	32	—	1.23	Ppt.	Carcinoma of gall bladder with hepatic involvement (A).
31	M. 31	10.4‡	+	30	—	0.93	Ext.	Pancreatitis with obstruction of common bile duct; surgical exploration and cholecystogastrostomy.
		None	None	—	124	3.21	Ext.	20 months later; clinically well; gained weight; moving furniture.
32	F. 62	160†	++++	34	—	1.25	Ext.	Carcinoma of stomach with metastasis to the liver.
33	F. 61	222†	++++	31	—	0.73	Ext.	Carcinoma of stomach (A).
34	F. 65	None	++++	34.9	—	1.70	Ext.	Carcinoma of stomach (X-ray).
35	M. 67	None	++++	30	—	1.19	Ppt.	Carcinoma of stomach (X-ray).
		None	++++	—	—	2.30	Ppt.	2 weeks later; no change clinically.
36	M. 39	None	++	32	—	1.94	Ppt. Ext.	Primary adenocarcinoma of liver (A).
37	M. 39	12.8‡	+++	21.4	110	2.22		Carcinoma of rectum with widespread metastasis to the liver (A).

two determinations were made by the precipitation method and the last by the extraction method. The results obtained in this case corresponded in every way with the clinical course. The second determination was made at the end of several months' hospitalization and the final observation was made 16 months after his release from the hospital. Clinically, the patient had regressed to the same level as at the time of the first determination.

Case 15 was operated upon because it was thought there was common duct obstruction. However, postmortem examination showed that the only pathology present was a marked cirrhosis. With a normal urea clearance in this instance the low hippuric acid output must be attributed to the extensive liver damage. In this case, the precipitation and titration method would have been very inaccurate as due to the very low output the amount of precipitate would have been very small, and the marked bilirubinuria would have made titration impractical. Death in this instance was a typical "liver death" due to failure of liver function postoperatively.

Table 3. This is a *group of cases affected with syphilis* and varying degrees of hepatic involvement. Two determinations were made in Case 16. The second was made 2 months after the first and, although the jaundice had greatly decreased, there was only a negligible increase in the output of hippuric acid. This would indicate that the decrease in jaundice does not necessarily indicate a similar improvement in liver function. This finding has been noted by both Quick and Vaccaro.

It is interesting to compare the histories of Cases 17 and 18. In each instance the patient became jaundiced following a single injection of neoarsphenamine. In Case 17 the liver function was normal and the history revealed that the patient had acquired syphilis only a few months previously. However, Case 18 gave a history of having been jaundiced following previous treatment and his syphilis was of several years' duration. In the latter case there was a lowered liver function with definite widespread liver damage, but in Case 17 the jaundice was probably due to an acute arsenical hepatitis of very recent origin.

In this group the results vary from limits of normal to 0.9 gm., the total four-hour output indicating the great variation in amount of liver damage produced by hepatic syphilis.

Table 4. This group is composed of cases of *malignant tumors* with widespread hepatic involvement as evidenced by clinical studies. All of the 4 cases which came to autopsy showed extensive metastases. Case 31, who was deeply jaundiced and whose liver function was extremely low, was operated for carcinoma of the head of the pancreas. After a stormy convalescence following a cholecystogastrostomy the patient recovered and at the present time is engaged as a furniture mover. Twenty months after his release from the hospital the patient returned for another liver function test and the output of hippuric acid was found to be normal. This patient had a reduced liver function as the result of prolonged obstructive jaundice but when the obstruction was relieved the detoxification mechanism returned to normal.

The results in this group were, on an average, the lowest of any obtained in this series.

Table 5. In this group are 22 cases of *disease of the biliary tract,* all of which were operated upon. The test results varied widely. In cases with normal liver function the postoperative reaction was mild and recovery was uneventful. Two deaths occurred in cases with low liver function. In each instance the clinical syndrome could be described as typical hepatic failure terminating in "liver death." A third death occurred

TABLE V

This is a group of cases of extrahepatic biliary disease, all of which were operated. The diagnosis given is the final diagnosis. The Wassermann was negative in all cases but Case 42

Case No.	Sex and Age	Jaundice	Blood N.P.N. mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment
38	F. 44	8.8†	30	—	2.32	Ppt.	Cholecystitis without stones; recovered.
39	M. 39	None	27.3	—	2.90	Ppt.	Cholecystitis without stones; cholecystectomy; recovered.
40	F. 42	None	30	—	1.76	Ppt.	Cholelithiasis; typical "liver death" following surgery.
41	F. 60	None	38	—	1.94	Ppt.	Cholelithiasis; this test taken preoperatively.
		None	—	—	1.78	Ppt.	3 months later, at end of stormy convalescence.
42	F. 46	None	30	—	2.08	Ppt.	Cholelithiasis; died following surgery; autopsy refused.
43	F. 54	49.4†	38	—	0.92	Ppt.	Cholelithiasis; test taken preoperatively.
		8†	—	—	2.74	Ppt.	2 months later; stormy recovery.
44	F. 35	None	30	—	2.27	Ppt.	Cholelithiasis; cholecystectomy; uneventful recovery; test taken preoperatively.
		None	—	—	2.52	Ppt.	1 month postoperative.
45	F. 45	None	30	—	3.20	Ppt.	Cholelithiasis; cholecystectomy; recovered.
46	F. 58	7.5†	35	—	3.07	Ext.	Cholecystitis without stones; cholecystectomy; uneventful recovery.
47	F. 50	35.0†	34	—	2.01	Ext.	Choledocholithiasis; cholecystectomy; obstruction of short duration.
48	F. 32	200† 9.4‡	32	—	0.901	Ext.	Cholelithiasis, with obstruction over a long period; direct van den Bergh; typical "liver death" following surgery.
49	F. 43	1.3‡	—	98	3.00	Ext.	Preoperative diagnosis cholelithiasis; postoperative diagnosis appendicitis.
50	F. 42	None	—	80	3.03	Ext.	Cholelithiasis; cholecystectomy; one large stone; uneventful recovery; mild postoperative symptoms.
51	F. 31	None	—	130	2.48	Ext.	Cholelithiasis; cholecystectomy; violent and prolonged postoperative course.
52	F. 25	3.1‡	40	72	1.26	Ext.	Choledocholithiasis; long period of obstruction; stormy recovery.
53	F. 40	2.0‡	—	82	3.20	Ext	Cholelithiasis; uneventful recovery.
54	M. 48	None	—	77	3.11	Ext.	Cholecystitis without stones; uneventful recovery.
55	F. 40	5.5‡	—	65	2.5	Ext.	Cholelithiasis; cholecystectomy; moderate postoperative symptoms.
56	M. 28	4.1‡	—	87	3.23	Ext.	Cholelithiasis; cholecystectomy; liver showed marked changes; uneventful recovery.
57	M. 49	7.5‡	—	96.5	3.30	Ext.	Cholelithiasis; cholecystectomy; uneventful recovery.
58	M. 28	None	—	94	3.70	Ext.	Cholelithiasis; cholecystectomy; uneventful recovery.
59	F. 59	None	—	69	2.65	Ext.	Cholelithiasis; cholecystectomy; uneventful recovery.

in a case with only moderate liver damage but which was complicated by syphilis. Other cases operated upon when there was low liver function recovered, but in all of these cases the convalescence was exceedingly stormy and accompanied by hyperpyrexia with nausea and vomiting. The results indicate that the severity of this postoperative reaction increases as the output of hippuric acid decreases.

In Cases 41, 43 and 44 tests were made after the patients had completely recovered from surgery. In none of these cases had the hepatic function, which had been lowered preoperatively, returned to normal. The excretion of hippuric acid had decreased in one instance. These results would indicate that in cases of cholelithiasis and cholecystitis surgery offers a much greater risk when there is evidence of an impaired detoxicating mechanism as shown by the hippuric acid test. Furthermore, surgical removal of the gall bladder does not serve to restore pre-existing hepatic damage, although it may serve to eliminate a source of furthering this damage.

Table 6. This group consists of 4 cases of *catarrhal jaundice.* All of these patients recovered, and the diagnosis was made from clinical study. As the precipitation method is considered very inaccurate in these

TABLE VI

All of these cases were diagnosed clinically as catarrhal jaundice and made uneventful recoveries. There was no history of lues or antiluetic treatment and the Wassermann was negative in each case

Case No.	Sex and Age	Jaundice	Hepatic Enlargement	Blood N.P.N. mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment
60	M. 60	4‡	None	—	124	3.38	Ext.	Normal liver; in relapse of pernicious anemia.
		20‡	None	—	—	1.68	Ext.	During acute catarrhal jaundice—3 months after first test.
61	M. 25	4‡	++	27	—	1.90	Ext.	Acute catarrhal jaundice; direct van den Bergh positive.
62	M. 25	75†	++	30	—	2.04	Ext.	Acute catarrhal jaundice; direct van den Bergh.
63	F. 40	103†	++++	28	—	0.764	Ext.	Acute catarrhal jaundice; severe hepatitis of unknown cause; two determinations run.
						0.988	Ext.	

severely jaundiced individuals all of these cases were studied with the extraction method.

Case 60 is particularly interesting because by chance this patient had had a hippuric acid test 3 months before the jaundice developed. At the time the first test was taken the liver function was normal but during the acute attack of typical catarrhal jaundice there was a marked reduction in excretion of hippuric acid.

Table 7. This is a small group of patients with *toxemia of pregnancy*, in all of which the hippuric acid output was reduced. The severity of clinical symptoms seemed to bear a definite relationship to the degree of liver damage as measured by this test. When the test was repeated during the post-partum period in Cases 66 and 67 each of these showed a marked increase in hippuric acid excretion. However, this problem is very complex and these results indicate only the need for further study of the hepatic detoxifying mechanism during pregnancy.

Table 8. This table includes a variety of *miscellaneous cases*, in each of which there was a decrease in urea clearance. Some of the patients showed clinical evidence of hepatic involvement plus renal damage, but others showed renal dysfunction only.

In Case 69 malignancy with metastasis to the liver was the preoperative diagnosis. Although nitrogen retention was not present the urea clearance was greatly reduced. The reduced hippuric acid output was probably due to poor renal function, as in surgery the liver appeared normal grossly and only a fibroid of the uterus was removed. Cases 72 and 76 showed no nitrogen retention and in Case 75 there was only slight retention, but the lowered urea clearance and the decreased hippuric acid output indicate the necessity for combining these two tests. Case 77 showed that nephritis alone without liver damage is capable of reducing the output of hippuric acid. Furthermore, there was no evidence of nitrogen retention, although the urea clearance was very low.

DISCUSSION

The fact that the urea clearance test can be combined with a liver function test so that both liver function and kidney function can be studied on the same urine specimens, increases the value of both tests to the clinician. The urea clearance is a better control for the hippuric acid test than is the simple measurement of nitrogen retention, because, as stated by Van Slyke, *et al* (9), "it is only when the renal function, as measured by the urea clearance, has fallen to less than 20% of normal that a great part of the blood urea

TABLE VII

This is a group of cases of toxemia of pregnancy. In Cases 66 and 67 tests were taken during both the prenatal and post-partum periods. In none of these cases was there jaundice, hepatic enlargement, or a positive Wassermann

Case No.	Sex and Age	Blood N.P.N. mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment
64	F. 33	24	106	2.40	Ext.	Mild toxic symptoms.
65	F. 35	28	68	2.33	Ext.	Definite toxemia; albuminuria plus hypertension.
66	F. 22	—	83	1.30	Ext.	Definite toxemia.
		—	—	2.03	Ext.	Taken 10 days post-partum; no signs of toxemia present.
67	F. 20	28	63	1.68	Ext.	Toxemia of pregnancy.
		—	—	2.12	Ext.	Taken 15 days post-partum; no signs of toxemia present.
68	F. 31	30	86	1.58	Ext.	Toxemia of pregnancy; albuminuria, headache, hypertension and vertigo.

TABLE VIII

All cases in this group had definite nephritis. Although only urea clearance test is given some of these cases showed reduction in other kidney function tests. The Wassermann was negative in each case.

Case No.	Sex and Age	Jaundice	Hepatic Enlargement	Blood Urea Nitrogen mg. per 100 c.c.	Urea Clearance % of normal	Benzoic Acid Excreted in 4 hrs. gm.	Method	Comment
69	F. 45	None	None	8.0	42	1.44	Ext.	Ascites; exploratory laparotomy done and large uterine fibroid removed.
70	M. 60	5.5%	++	—	41	2.01	Ext.	Pancreatitis; cholecystostomy autopsy diagnosis.
71	F. 60	30%	++—	—	41	1.17	Ext.	Jaundiced for some time; albuminuria and fixed specific gravity; refused surgery.
		1%	?	—	—	1.37	Ext.	Jaundice completely cleared; no evidence of hepatitis; 3 months after first test.
72	F. 61	100%	+++—	7.8	50	0.841	Ext	Hepatitis.
73	F. 32	3%	None	84.8	38	0.826	Ext.	Marked nephritis; patient became jaundiced during antiluetic treatment.
		0.5%	None	—	—	0.796	Ext	No visible jaundice; patient greatly improved clinically.
74	F. 51	10%	+++—	—	29	1.00	Ext.	Inoperable carcinoma of the stomach; died soon after exploratory laparotomy
75	F. 62	None	None	25.6	39	1.86	Ext.	Pernicious anemia; no evidence of liver damage but patient had a definite nephritis.
76	F. 55	None	None	15.8	46	1.59	Ext.	Pernicious anemia, advanced nephritis.
77	F. 46	None	None	11.4	25	2.00	Ext	No evidence of liver disturbance; marked nephritis

concentrations become definitely elevated." (See Case 77).

This *combined liver and kidney function test* offers an added safeguard in the preoperative study of surgical cases, because postoperative complications which may result in the so-called "liver death" are most likely to occur in those cases in which the hepatic detoxifying mechanism or the renal function is impaired. The exact mechanism which brings about the syndrome terminating in "liver death" with its accompanying disturbances in metabolism is unknown. However, the fact remains that there is a combined failure of hepatic and renal functions in these cases. Helwig and Schutz (10) suggested that the pathogenesis of this syndrome depends primarily on some intracellular hepatic damage. They believe a toxin is the causative factor and that this toxin may be produced by a perversion of functions of the damaged liver cells or by a lack of the proper physiological detoxifying ability of the cells. This failure of hepatic detoxification would thus permit the accumulation of substances which are toxic to the kidney. The presence of a low four-hour output of hippuric acid with a normal urea clearance would indicate that the liver is unable to synthesize sufficient glycine during this period. However, when the urea clearance is less than 50% of normal the diminished output of hippuric acid may be due to kidney damage as well as to hepatic damage. When there is a low hippuric acid excretion or low urea clearance the case should be considered a poor surgical risk, especially when the surgery would involve the extrahepatic biliary system.

The tests described are of equal importance to the internist in his study of diseases of the liver. A knowledge of the degree of impairment of the detoxifying mechanism of the liver is essential whenever the use of hepatotoxic drugs is contemplated. As shown by Wile and Sams (11), the low incidence of jaundice in untreated syphilis (0.18%) as compared with that (1.37%) following arsphenamine treatment indicates the high degree of hepatotoxicity exerted by this drug. Posttherapeutic jaundice is most likely to occur in cases in which there is pre-existing damage of the detoxifying mechanism as indicated by the hippuric acid test. A low output of hippuric acid would therefore be a contraindication for the use of arsphenamine in the usual manner.

The hippuric acid test offers also a means of determining the progress of cirrhosis and of other diseases of the liver. This test is a more accurate method of determining the recovery from hepatic disease with jaundice than is the determination of the serum bilirubin. This variation between the rate of disappearance of jaundice and the recovery of the detoxifying ability, as previously reported by Quick, is borne out by studies made on the cases in this series.

The results reported in the present series of cases are similar to those obtained by the other investigators. However, the hourly determination of hippuric acid is not of great clinical value and for general use the single determination of the total four-hour output is sufficient.

SUMMARY AND CONCLUSIONS

1. The hippuric acid test was used in a series of 77 cases. The results indicate that there may be a marked reduction in the detoxifying ability of the liver before

any of the clinical signs of hepatic disease can be detected.

2. The simultaneous determination of the urea clearance increases the value of the hippuric acid test.

3. The ether extraction method with the formol titration is the most practical as well as the most accurate method of determining the hippuric acid in the urine.

4. The combined urea clearance and hippuric acid test is a reliable and valuable adjunct in the study of hepatic disease.

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The Relation of Gastric Acidity to the Erythrocyte Content of the Blood*

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IN 1931 it was shown by Apperly and Crabtree (4) that the concentration of hydrochloric acid in the human stomach after a test-meal was regulated by the CO_2 content of the plasma of the fasting subject. This was found to be true not only when the plasma CO_2 was artifically varied in the subject of experiment, but also when different normal individuals were compared. A recent survey of all available clinical data relating to conditions in which plasma CO_2 varied within and beyond the normal limits has entirely confirmed the above experimental results. (Apperly, 1936) (3). Among these is the group of anoxemic conditions, of which anemia has special interest.

It has long been felt that anemia tends to lower both gastric acidity and plasma CO_2. Our preliminary experiments, however, showed us that in anoxemia, gastric acidity was considerably lower than could be accounted for by the fall of plasma CO_2. It appeared that anoxemia was of itself able to lower gastric acidity, and even result in achlorhydria. This raised the question, viz. Is there an anemic achlorhydria in contrast to the achlorhydric anemia of Witts? These considerations led us to investigate gastric acidity over a wide range of red cell content of blood.

A. *Relation of gastric acidity to red cell content of blood in normal people.*

The first interesting fact that we noticed was the striking similarity between the graph representing the average gastric acidities for different age and sex groups (as determined by Vanzant, Alvarez, *et al* (11) from 3746 cases), (Fig. 1), and the graph showing the average hemoglobin content of the blood for similar age and sex groups (from Peters and Van Slyke) (10), (Fig. 2). When the figures from these two series of observations are plotted against each other a straight line relationship is revealed, (Fig. 3). There is, of course, a considerable individual scattering about these average curves. These charts suggest two things: (a) That variations in average gastric acidity for different age and sex groups are at least partly dependent on hemoglobin differences, or whatever causes the latter, and (b) That, assuming the straight line in Fig. 3 continues as such to the base line, gastric acidity disappears when the hemoglobin of the blood falls to an average of about two-thirds its normal value; that is, that anemia can bring about achlorhydria. These figures, however, show us the relationship of gastric acidity and hemoglobin only over the range found in normal people. What happens in anemia and polycythemia?

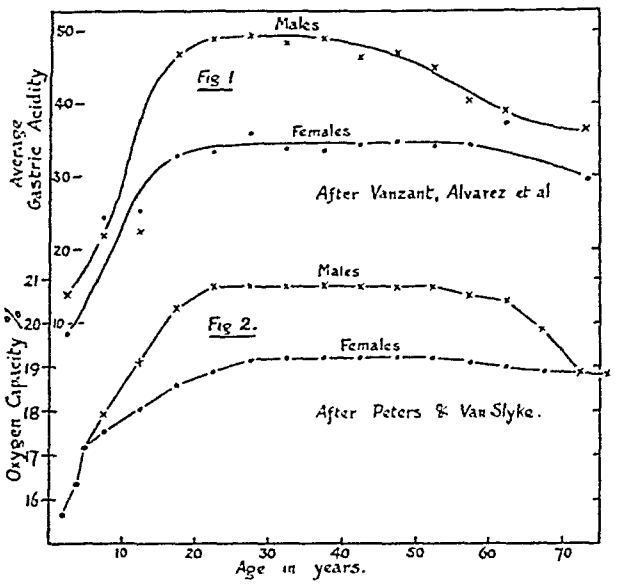
B. *Relation of acidity to red cell content in hemorrhagic anemia.*

For our study of gastric acidity in anemia we chose afebrile cases of recent and chronic hemorrhage, since it appeared to us that these were of the simplest type, uncomplicated by hypochromia, toxic or other factors of which the effects were unknown. In all cases red cell volume (hematocrit) and gastric acidity at one hour (gruel meal of 400 c.c. and Rehfuss tube) were determined in the resting and fasting patient on different occasions, e.g. on admission, during hospitalization and sometimes after discharge. As Fig. 4 shows, although the acidity is far from being the same in different individuals with the same erythrocyte volume, in all cases acidity rises with increase in red cell volume. In some cases achlorhydria accompanied the lower erythrocyte levels. (Three cases with gastric symptoms and high acidity referred to later are omitted from Fig. 4).

In all examinations the blood was drawn from the median-basilic vein under oil to prevent loss of CO_2 and therefore changes in pH and red cell volume. It was then defibrinated by the technique of Eisenmann

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(shaking with mercury without contact with air) and centrifuged for one hour at 3000 revolutions per minute in the hematocrit tubes of Shock and Hastings. This speed gives constant readings after 40 minutes.

C. *Relation of acidity to red cell content in polycythemia.*

Our own figures from cases of polycythemia in man are too few to make definite generalizations. Our four cases, however, all have a low acidity (Fig. 4). If this is typical, then it would appear that at, or just beyond the normal hemoglobin content the acidity curve falls again. There is very little record in the literature of the relationship of polycythemia to gastric acidity and what there is mostly relates to these conditions in association with duodenal ulcer. The following appear to have most bearing on our problem:

a. Wilbur and Ochsner (12) examined the gastric acidity in twenty-five cases of polycythemia of which five had duodenal ulcer. The figures of each case are not given, but of the non-ulcer cases, the acidity in sixteen fell within normal limits, and in four there was hypochlorhydria or achlorhydria. All of the five ulcer cases, however, showed hyperchlorhydria, one rising to a free acidity of eighty.

b. Friedman (5) has collected twenty-seven cases of duodenal ulcer with polycythemia in all of whom there was a hyperacidity which increased with increasing polycythemia.

c. Lerman, Pierce and Brogan (9), in a series of two hundred patients with no gastric symptoms showed a steady rise of acidity with red cell count up to seven millions. They used a meal of fifty c.c. of 7% alcohol and a simultaneous injection of 0.5 mgm. histamine, so that beyond their general effect these results can hardly be compared with the ordinary test-meal figures.

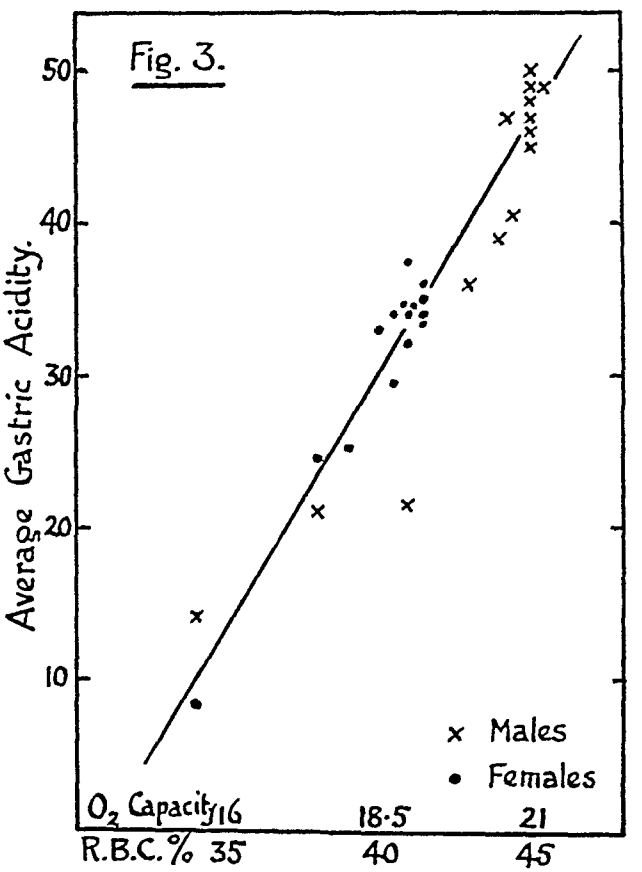
d. Fouts, Helmer and Zerfas (6) have published a number of cases of anemia of different types in which red cell counts, hemoglobin and the *highest* titratable acid are recorded, but no relationship was disclosed. The work of the authors quoted in the preceding paragraphs and our own experience indicate that these relationships are only revealed when the acidity in each case is determined at the same time, e.g. at one hour, after the ingestion of the test-meal, and not at that time at which the acidity is at its highest.

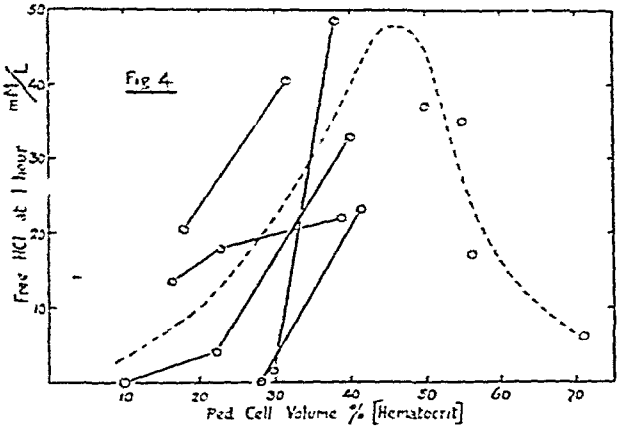
The work quoted above at first sight seems to be conflicting. We can divide the various cases into two groups, viz. (1) Those polycythemic patients with no gastric symptoms who were tested by the Ewald or gruel meal. In these the acidity was normal or low (our own four cases: Wilbur and Ochsner's twenty cases), (2) Those polycythemic patients who had, in addition, duodenal ulceration (the groups of Friedman and the remaining five cases of Wilbur and Ochsner). In these cases acidity continued to rise with increasing polycythemia.

From the above somewhat scant evidence then, it will be seen, when we put aside all cases complicated by peptic ulcer or other gastric abnormalities and consider only those remaining cases in which the same bland test-meal was employed (such as that used by Alvarez, Wilbur and ourselves) that with increasing polycythemia gastric acidity falls. Since, however, this evidence is so meager, we decided to carry out experiments on dogs.

D. *Experimental observations on anemia and polycythemia in dogs.*

Observations were made on five dogs in which anemia and polycythemia were produced by bleeding and transfusion. In order not to alter significantly the blood volume or osmotic pressure by these procedures the following technique was used. Sufficient blood was drawn in several fractions from the femoral artery to produce the required amount of anemia. The serum was then centrifuged from the cells, made up to a slightly greater volume than the original whole





blood and reinjected into the animal within an hour of bleeding. To produce polycythemia the cells were suspended in as little saline as compatible with a slow flow by gravity, and injected into another animal. The dogs were kept on a constant diet of prepared food (Purina Chow) containing all the necessary vitamins and minerals. Under this regime they lost no weight and were lacking in energy only at the lowest cell volumes (below 18%). At the very highest cell volumes (70% or more) there was a tendency to a mild diarrhea, somewhat blood streaked. This disappeared within 48 hours after the cell transfusion.

In dog 5, there were exceptions to this routine. In order to prevent the rapid regeneration of blood on the stock diet, which necessitated very frequent bleedings, this dog was kept on a bread, milk, and cod liver oil diet during the anemic phase. This enabled us to make several determinations at any blood level. A few meals of stock diet would raise the blood level and allow study at the next level.

Two days were allowed after bleedings or transfusions for the blood electrolytes to settle to a new equilibrium. Blood was then drawn from the jujular vein, treated as in section B, above, and the hematocrit volume determined. The Rehfuss tube was then passed into the stomach, the dog lying quietly on its back, or left side, fasting contents withdrawn and a volume of 5% alcohol in water (9 c.c. per kilo) run into the stomach. Samples were withdrawn every fifteen minutes for titration of free acid.

The results of these experiments are shown in Fig 5. It will be seen that in every case gastric acidity at 30 minutes after the alcohol "meal" rises with erythrocyte content of blood to a maximum at a point somewhat above the normal erythrocyte content. Beyond this point gastric acidity falls. These results then are in keeping with those found in man as described above.

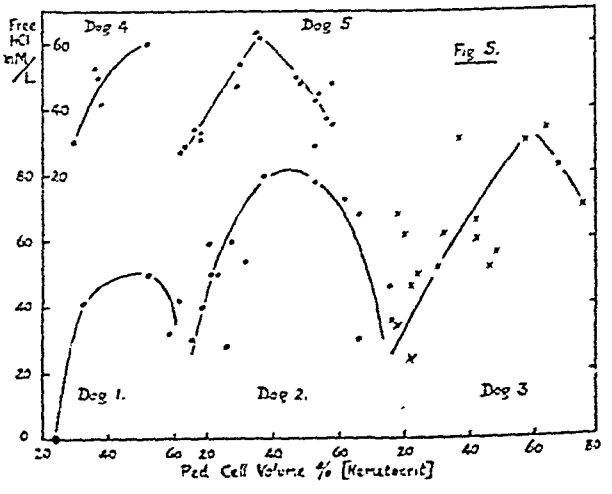
In presenting these results we should add some comments. Certain conditions which we could not always explain or control occasionally caused exceedingly rapid or slow emptying of the stomach, with consequent changes in acidity. We feel justified in using the data only from those experiments in which the emptying time was "average" and rejecting the extremes, i.e. those with emptying time of less than 45 minutes and more than 90 minutes. We also rejected a few cases when an excessive regurgitation of bile occurred in animals in which some bile did not habitually appear. The first three tests on all dogs were also discarded, because we felt that the restlessness and nervous apprehension accompanying the unaccustomed technique caused the achlorhydria usually found. Further, in the first few experiments small dogs were chosen in order that the desired degree of anemia or polycythemia could be produced by the withdrawal or transfusion of smaller volumes of blood, but the small size of the arteries and veins in these animals presented an almost insuperable obstacle. Consequently in these cases (Dogs 1 and 4) only a few points are plotted. Of themselves they would have little significance, but they are presented as additional evidence to the more complete curves obtained from the other dogs. In one animal (Dog 3) of highly excitable temperament, used during the late summer and early fall, when the temperature was very variable and respiration obviously affected, the points are very scattered on the anemic end of the curve. Those on the polycythemic end, taken later at a more constant temperature and with no exciting factors (such as visitors or a strange attendant) show however the usual configuration.

E. *The incidence of achlorhydria in anemia and polycythemia.*

If our thesis is correct, viz. that the highest acidity in any individual accompanies a normal red cell content, but diminishes with increasing anemia or polycythemia, then we should expect to find in any group of people a higher incidence of achlorhydria among those with anemia and polycythemia, the achlorhydria incidence increasing with increasing severity of these conditions. This has indeed already been demonstrated by Lerman and Means (8) and by Alvarez (2). These observations therefore support our own work.

F. *Relation of gastric acidity to red cell content of blood in association with gastric abnormality.*

It is well known that gastric acidity is regulated by, among other factors, duodenal regurgitation. Anything which interferes with this, e.g. pyloric spasm, or the over-rapid hypertonic stomach, results in hyperacidity. Under these circumstances we would expect, even in severe anemia or hyperchlorhydria, an acidity higher than that normally corresponding to the red cell content of the blood. The work of Friedman (5) and of Wilbur and Ochsner (12) quoted in section C. above shows that this is so. This has also been the experience of Hurst (7), Alvarez (1) and ourselves. Among our cases there were three (bleeding duodenal ulcer: pylorospasm: nervous hypermotility) in all of



whom there was, in spite of severe anemia, a marked hyperacidity. With improvement in the blood condition acidity in all three rose still higher. With eventual disappearance of symptoms in the case of duodenal ulcer the acidity fell to a "normal" figure at the third examination. It will be recalled that higher acidities were also found in one of our dogs (dog 3) when a nervous hypermotility was associated with the presence of strangers in the laboratory.

SUMMARY AND CONCLUSIONS

These observations show that:

(a) When, as a result of recent or chronic hemorrhage, the red cell content of the blood falls below a certain critical level, free acid disappears from the stomach. Our results in a few cases in man indicate that this level is, on the average, about one-third to two-thirds the normal. In dogs the critical level is much lower. We have no information concerning gastric acidity in anemias of other origins.

(b) Above this critical level gastric acidity rises with erythrocyte content to a maximum when the latter somewhat exceeds that found in normal health, i.e. in man, a hematocrit volume of 46%.

(c) With increasing hematocrit volumes above about 50%, in man and dogs, acidity steadily falls again to low figures.

(d) From the above we would expect a rising incidence of achlorhydria with increasing anemia and increasing polycythemia. This has been shown to be so by several observers.

(e) When severe hemorrhagic anemia is associated with peptic ulcer, pylorospasm or certain other gastric conditions, acidity values are found to be far higher than those with a corresponding degree of anemia without gastric abnormality.

(f) Our experiments show that in certain conditions where anemia is associated with achlorhydria, the entity which we have called anemic achlorhydria must be considered in addition to Witts's achlorhydric anemia and pernicious anemia.

Note: We are indebted to the Richmond Dairy Co. for the donation of the milk used in the dog experiments.

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The Intestinal Rate, Normal Nutrition, and Health:

New Principles for the Maintenance, Restoration, and Control of Health

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INDIGESTION, MALNUTRITION AND DISEASE

"THE wonder is not that structural imperfections and functional disharmonies should develop in proportion to our numbers, but rather that so many of us escape harm altogether and enjoy good health. . . The solution of our problem of life is a fuller knowledge of the use and working of those parts of our bodies most apt to give way under our modern ways of living—the use of such structures as the great bowel. And when we have replaced our ignorance by real knowledge, we shall be in a position not to adapt our bodily structure to our mode of living, but our mode of living or our bodily structures. . . The great bowel is not a useless or superfluous organ, but one which we in our ignorance are maltreating" (1).

Such an assertion intimates that intestinal indigestion, malnutrition and ill health may be revealed by a better understanding of the functions of the colon from right eating; and they may be corrected by an exact means to determine the absorption of food; for "little is known concerning the difficulties of absorption and utilization of food products from the digestive tract, and regarding what particular foods may improve gastro-intestinal function. . . It is probable that significant degrees of such disturbances may arise in arthritis, and be overcome by well chosen diets" (2).

Obviously, eating too fast and too much, irregularly, incomplete or disproportioned meals, or the frequent use of laxatives, etc., are not conducive to the maintenance of normal nutrition and health. But when "we adapt our mode of living to our bodily structures" by the correction of these erroneous ways, a delicately adjusted and complex function of the colon begins to operate, which moulds the intestinal contents entirely

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into the uniform segments of the normal feces. In this way the digestive system acts as a perfect nutritive apparatus, because this function serves to determine wrong eating, and perhaps erroneous ways of living. Again, as this function moulds the normal feces, it also measures the contribution made one meal to the construction of the body, or the normal intestinal rate;* and thus these indices denote the complete digestion and absorption of the food (3). Then, as nutrition is the sum of the processes by which an animal absorbs, utilizes, and takes in food substances, and assimilation is the final and most important phase of the process (4), the indices of absorption still further serve to determine normal nutrition, and to furnish a clue to the construction and maintenance of cells. For by the application of these indices to nutrition, erroneous ways of eating not only provoke a previously unrecognized kind of intestinal indigestion and malnutrition, but also give rise to a formerly obscure cause of disease. This is because they result in a course, incomplete, and disportioned alimentary mixture, which induces an abnormal action of the colon, by which soft and formless feces and rapid intestinal rates are produced. In these circumstances nourishment goes *through* instead of *into* the body, and the relatively unknown condition of an exact and improved state of well being from normal or anabolic nutrition cannot be maintained. In such a disorder there is a failure in the final and most important phase of nutrition—assimilation—and the weak skin, bone, or some other tissue of a patient breaks down in a recognized metabolic disease. After some of these diseases, as indigestion, acne, eczema, psoriasis, or arthritis have been diagnosed, principles of treatment for the creation and control of this state of health to cure them, have been applied with good results (5, 6, 7, 7b).

THE CREATION OF ANABOLIC OR NORMAL NUTRITION

The correction of intestinal indigestion and malnutrition from this point of view, is brought about by teaching patients how and what to eat and how to live, so that their nutritive apparatus produces normal feces and normal intestinal rates. In carrying out these principles, an enquiry of the patient's ways of eating is first made, and one or more unhygienic habits are invariably revealed. And an examination of the feces at this time often confirms some of these erroneous ways of eating. Then, an explanation of the normal and abnormal operations of the nutritive apparatus with diagrams and descriptions of the normal, formed, and soft types of the feces with illustrations, are given. As a supplementary aid in learning the subject, a printed outline of the principles and practice, and a form to follow in keeping a record of nutrition, is presented to each patient. Again, the health measures advised, such as "to chew food thoroughly and eat dinner at night," or "to omit laxatives, eat fruit at lunch and dinner, and try to deject twice," are written out on a sheet for the patient to use for a record of his nutrition: and the supplementary measures to relieve symptoms are prescribed. After the patient has written out the food consumed, the time spent at meals, the time and kind of dejections, and a test of the intestinal rate, in a week's record, he returns to the office or health class with one often beginning like Record 1.

Record 1

Health measures to improve: eat slowly and dinner at night; also omit laxatives, eat fruit at lunch and dinner, and try to deject twice.

Thursday, September 27, 1934

6:30 to 6:50 p.m., beef broth, steak, beans, beets, toast, apple sauce, cake.

7:00 p.m., charcoal taken to mark this meal.

Friday

7:45 to 8 a.m.; egg, toast, coffee.

9:15 a.m., soft dejection with first charcoal; *initial intestinal rate, 14 hours.*

12:15 to 12:35 p.m., fish chowder, crackers, apple pie.

6:30 to 6:55 p.m., potato soup, cod, lima beans, broccoli, roll, peaches, cake.

Saturday

7 a.m., soft dejection with charcoal.

8 to 8:20 a.m., oatmeal, egg, toast, coffee.

1 to 1:20 p.m., vegetable soup, crackers, carrots, prunes, cake.

6:15 to 6:40 p.m., bouillion, chicken, potato, squash, spinach, roll, plum tart.

Sunday

8:30 to 8:50 a.m., creamed toast, fish ball, coffee.

10 a.m., soft dejection with last charcoal; *final intestinal rate, 63 hours.*

1:30 to 2:05 p.m., beef, potato, parsnips, cauliflower, roll, raspberry ice, cake.

6:30 to 6:50 p.m., cheese souffle, vegetable salad, roll, cocoa, peaches, cookies.

Monday

7:30 to 7:45 a.m., egg, corn bread, coffee.

9 a.m., soft dejection without charcoal.

12:30 to 12:50 p.m., omelette, potato, blueberries, cake.

6:45 to 7:15 p.m., beef, sweet potato, corn, peppers, toast, apple betty.

Discussion of Record 1:

The dejections noted by the patient in his first record are generally of the soft type; and the marked evening meal in passing through the nutritive apparatus in 14 to 63 hours, signifies a rapid intestinal rate. The former erroneous ways may have caused an irritable colon and malabsorption; but some foods should be increased and others should be reduced. Accordingly, still more health measures are advised, such as "to eat many vegetables and sparingly of meat, cereal foods and fruit"; and these are written out on a second sheet for a record of his nutrition. These measures should be adopted immediately, but another week's record may not be examined for two weeks. At this visit the patient generally feels better, although he may have lost a few pounds; but he has had some formed instead of soft dejections, and his intestinal rate has become a little more extended to one of about 14 to 85 hours. These changes indicate that a better alimentary mixture has begun to improve the action of the colonic functions and the absorption; and now the consumption of a small breakfast and lunch may be advised, in order still further to improve the utilization of food. These changes are shown in Table I.

From now on the patient should be seen every few weeks in order to observe his condition and weight.

*The intestinal rate is determined by the ingestion of 25 to 50 c.c. of French millet seeds or 100 grains of charcoal immediately after an evening meal; and then the number of hours that elapse from the time the marker was taken to the time when the seeds or charcoal are first and last seen in the feces, is observed. In adults producing segmented feces, one and sometimes two dejections are common daily, yet the marked evening meal takes about 62 hours to appear in, and 134 hours to disappear from the feces; and this rate is considered normal. (Burnett, F. L.: *Am. J. Roentgenol.*, 10:359, 1923).

TABLE I

The cure of disease by the creation and control of an improved state of well being in patients from anabolic or normal nutrition

Initials of Patients	Age	Sex	Disease and Its Duration	Erroneous Ways Excesses, or Deficiences of Food Consumption	Condition, Weight, Feces and Intestinal Rate During Treatment (The four items are listed consecutively)				
					1st week	2nd month	6 months	1st year	2nd to 4th years
F. A.	41	F.	Arthritis hypertrophic 10 yrs.	Laxatives + fruit +	Same, 135 lbs. Soft, 12-60 hrs.	Same, 136 lbs. Normal, 86-123 hrs.	Better. Normal, 87-144 hrs.	Well, 138 lbs. Normal, 38-132 hrs.	
J. P. B.	38	M.	Arthritis hypertrophic 8 yrs.	Fast +, vegetables —, ments +, cereals +	Same, 150 lbs. Soft, 13-63 hrs.	Same, 147 lbs. Formed, 39-110 hrs.		Well, 167 lbs. Normal.	
I. F.	54	F.	Arthritis atrophic 1 yr.	Irregular +, fast +, foods +	Same, 151 lbs. Soft, 20-38 hrs.	Better, 150 lbs. Normal, 39-144 hrs.	Better, 149 lbs. Normal, 37-159 hrs.	Well, 147 lbs. Normal, 38-143 hrs.	Well, 145 lbs. Normal, 38-143 hrs.
T. O'B.	31	M.	Arthritis hypertrophic 2 yrs.	Fast +, fruit +, irregular +	Same, 148 lbs. Soft, 36-67 hrs.	Same, 145 lbs. Normal, 36-136 hrs.	Better, 144 lbs. Normal, 38-133 hrs.	Well, 142 lbs. Normal, 39-134 hrs.	Well, 150 lbs. Normal, 61-120 hrs.
M. McL.	35	F.	Arthritis atrophic 1 yr.	Fast +, irregular +, sweets +, cereals +	Same, 174 lbs. Soft, 14-51 hrs.	Same, 163 lbs. Formed, 25-108 hrs.	Better, 162 lbs. Normal, 38-120 hrs.	Well, 161 lbs. Normal, 39-122 hrs.	Well, 158 lbs. Normal, 39-120 hrs.
R. R.	28	F.	Psoriasis, 15 yrs. and arthritis, 5 mos.	Irregular +, sweets +, fruit +, laxatives +	Same, 138 lbs. Soft, 38-86 hrs.	Better, 134 lbs. Formed, 38-110 hrs.	Better, 129 lbs. Normal, 61-110 hrs.	Well, 133 lbs. Normal, 63-132 hrs.	Well, 145 lbs. Normal, 62-132 hrs.
A. T.	46	F.	Eczema, 4 yrs.	Fast +, irregular +, sweets +	Same, 139 lbs. Soft, 25-109 hrs.	Better, 134 lbs. Formed, 43-114 hrs.	Better, 119 lbs. Normal, 39-134 hrs.	Better, 122 lbs. Normal, 76-134 hrs.	Well, 134 lbs. Normal, 60-134 hrs.
W. O. S.	39	M.	Iritis, 6 yrs.	Fast +, irregular +, cereals +	Same, 208 lbs. Soft, 15-38 hrs.	Better, 187 lbs. Soft, 17-92 hrs.	Better, 171 lbs. Soft, 17-95 hrs.	Well, 166 lbs. Formed, 42-92 hrs.	Well, 146 lbs. Normal, 43-114 hrs.

but more particularly to examine records of his nutrition; for unless he presents records showing one or two normal dejections daily, and rates of 38 to 110 hours or better, his alimentary mixture is not refined enough, and the health measures must be carried out more precisely. As the intestinal rate is the most exact means to determine normal nutrition, all patients are advised to make this test and to weigh the body every few weeks; and those who carry out these requirements, have normal rates, and change little in weight, can be seen infrequently. At one of these visits, an examination of the patient's blood for anemia or hypoglycemia, or tests for other conditions, can be made.

THE CURE OF DISEASE BY THE CREATION AND CONTROL OF AN IMPROVED STATE OF WELL BEING

The results obtained from the education of about a thousand patients with symptomatic indigestion, acne, eczema, psoriasis, arthritis, or some other disease, to restore health from anabolic nutrition, have been gratifying; because when the principles of treatment are understood and cooperation of the patients is secured, the diseases are almost invariably relieved. To be sure, the improvement in the health of chronic invalids is always slow, and months and sometimes years of treatment are required before tangible results become evident. The results obtained in the treatment of all of these diseases are very similar; therefore, definite figures of those compiled in a recent study of arthritis (7), may be used for this purpose.

In this study, an attempt was made to educate 241 patients in these principles of treatment, over a period of five years. Of this number, 74 were private and 167 charity patients; but there were 34, in the latter group especially, who were unable to understand the practice of anabolic nutrition, and there were 89, who by a failure to bring in more than five records or to be observed for more than five months, were considered uncooperative; and the patients of these groups have been excluded in an appraisal of the treatment. Of the remaining 118 patients, 45 became healthy, in as much as they were free of pain and swelling in the joints, and enjoyed a normal sphere of activity, and 73 became better. Some of these became healthy subsequently by more prolonged treatment; and 7 of this number made an attempt to learn anabolic nutrition once and failed, then took up treatment again after remaining the same or becoming worse for a year, and have improved. Details of the results of treatment in a few patients with arthritis, and other diseases are shown in Table I.

When disease is relieved by the creation of an exact state of health, it is obvious that a recurrence must be prevented if the disease is to be cured. All persons are human and are likely to digress from the even and sometimes dull tenor of healthy living; and such digressions if of short duration and infrequent, may not be injurious when a reserve of health has been established. To prevent a recurrence of disease in these former patients, it is necessary to know from time to time how well they carry out the requirements of anabolic nutrition, in order to remain healthy. To this end, all of those instructed in the principles of treatment are advised to observe every dejection and to keep them normal, and to make a test of the intestinal rate and to weigh the body every few weeks, and

record them. Then, several times a year according to the supervision required, they are asked to bring in records of their nutrition. The response to such a request is shown in Record 2. And at one of these visits, a comprehensive and exact examination of the body and various specimens can be made, to assure these persons of good health. A few of the patients who were restored to health, and then failed to carry out the requirements to control their health and prevent a recurrence, are shown in Table II.

TABLE II

The recurrence of disease in healthy persons from a failure to control health from anabolic or normal nutrition

Initials of Patients	Age	Sex	Disease and Its Duration	Erroneous Ways, Excesses or Deficiencies of Food Consumption	Condition, Weight, Feces and Intestinal Rate (Listed Consecutively)		Comments on the Causes of the Recurrence of Disease
					1st week	2rd to 4th years	
A. M. S.	25	F.	Psoriasis, 9 yrs. and arthritis, 1 yr.	Laxatives +, fat +, cereal foods +	Same, 186 lbs. Formed, 56-111 hrs.	Well, 178 lbs. Normal, 51-124 hrs.	After two years of health began to eat too fast and too much fruit, failed to observe feces or determine intestinal rate, and had a *recurrence* of both diseases. Weight 158 lbs., feces soft, and intestinal rate 13-48 hrs.
G. N.	46	F.	Arthritis, 10 yrs.	Laxatives +, and cereal foods +	Same, 145 lbs. Formed, 60-134 hrs.	Well, 148 lbs. Normal, 63-111 hrs.	After a year of health, while travelling, ate irregularly and too fast, failed to determine rate or observe feces, and had a *recurrence*. After returning home ate better. Weight 145 lbs., feces formed, and intestinal rate 51-111 hrs.
F. A. R.	65	F.	Arthritis, 8 yrs.	Fast −, fat +, laxatives +	Same, 124 lbs. Soft, 14-87 hrs.	Well, 134 lbs. Normal, 48-110 hrs.	After two years of health in a country home moved to the city and ate out, fast, and too much fruit. She failed to observe feces and determine rate, and had a *recurrence*. Weight 128 lbs., rate 12-70 hrs.
L. N.	25	F.	Psoriasis, 20 yrs.	Fast −, laxatives +, vegetables −	Same, 124 lbs. Soft, 14-87 hrs.	Well, 115 lbs. Formed, 48-110 hrs.	After a year of health ate too fast and too much cereal food, observed *soft feces*, and had rates of 12-62, and 15-87 hrs. Shortly afterward, had a *recurrence*. Weight 107 lbs., rate 13-72 hrs.
W. O. S.	39	M.	Iritis, 6 yrs	Fast −, irregular −, cereals +	Same, 208 lbs. Soft, 15-38 hrs.	Well, 146 lbs. Normal, 43-114 hrs.	After three years of health went off on a vacation and ate too much and too fast, had soft feces and rate of about 17-67 hrs. shortly afterward had a *recurrence*. Weight 144 lbs., rate 36-87 hrs.

Record 2

Health measures to continue: to eat slowly, of a small breakfast and lunch, but a substantial dinner; also eat many vegetables and fruit according to absorption. Then determine rate and weight every few weeks and bring in a complete record of nutrition in January.

	Rate	Weight
Oct. 25	41 to 132 hrs.	132 lbs.
Nov. 8	65 to 134 hrs.	134 lbs.
Nov. 22	65 to 128 hrs.	133 lbs.
Dec. 6	40 to 114 hrs.	134 lbs.
Dec. 21	63 to 130 hrs.	135 lbs.
Jan. 4	62 to 127 hrs.	135 lbs.

Wednesday, January 17, 1935

6:50 to 7:25 p.m., steak, potato, beets, string beans, roll, chocolate pie.

7:30 p.m., seeds taken to mark this meal.

Thursday

7:30 to 7:15 a.m., bran muffins, tea.

9 a.m., normal dejection.

1:05 to 1:25 p.m., beef stew, cracker, apple pie.

6:55 to 7:25 p.m., potato soup, chicken, potato, squash, spinach, rice pudding.

Friday

7:45 to 8 a.m., toast, tea.

9:20 a.m., normal dejection.

1:10 to 1:25 p.m., fish chowder, cracker, apple sauce, cookies.

7 to 7:25 p.m., chicken soup, lamb, potato, parsnips, broccoli, roll, orange sherbert and cake.

10:45 p.m., normal dejection.

Saturday

8 to 8:20 a.m., corn bread, coffee.

9:30 a.m., normal dejection with first seeds; *initial intestinal rate, 62 hrs.*

1 to 1:20 p.m., scrambled eggs, bacon, lima beans, cut up oranges, cake.

7 to 7:25 p.m., oyster stew, sweet breads, potato, cauliflower, brussels sprouts, bread pudding.

Sunday

8:30 to 8:50 a.m., brown bread, coffee.

10:30 a.m., normal dejection with seeds.

1:30 to 1:50 p.m., cheese omelette, vegetable salad, crackers, peach pie.

6:30 to 7 p.m., beef, potato, beets, egg plant, roll, prune whip, cake.

Monday

7:30 to 7:50 a.m., toast, marmalade, tea.

1:05 to 1:20 p.m., lamb stew, bread, baked apple.

3:15 p.m., normal dejection with seeds.

6:45 to 7:15 p.m., beef broth, cod, sweet potato, turnips, celery, roll, Indian pudding.

11 p.m., normal dejection with seeds.

Tuesday

7:35 to 7:50 a.m., wheat muffins, tea.

10:30 a.m., normal dejection with last seeds; *final intestinal rate, 135 hrs.*

1 to 1:25 p.m., fried egg, fried potatoes, roll, mince pie.

6:55 to 7:30 p.m., celery soup, veal, potato, beans, spinach, roll, tapioca.

Wednesday

7:30 to 7:50 a.m., corn muffins, tea.

9:30 a.m., normal dejection without seeds.

1 to 1:15 p.m., veal stew, roll, prunes, cake.

7 to 7:25 p.m., duck, apple sauce, potato, peas, string beans, squash pie.

THE NORMAL NUTRITIVE APPARATUS, THE INTESTINAL RATE AND ASSIMILATION

Through the wisdom of the body as the circuit of the blood is influenced by sleep, rest, food, exercise, affections of the mind, and the like (8), so must the cycle of digestion and absorption be influenced by similar factors. Again as the work and performance of the heart are adapted to the needs of the body (8), so must the work and actions of the nutritive apparatus be adapted to the requirements of the bodily tissues for sustenance. Thus, the nutritive apparatus operates automatically and with reasoning, and these qualities are exhibited in the digestive pouches especially; for proper food in the primary pouch, the stomach, is normally churned to promote mixing, digestion and partial absorption of the aliment, but very unsuitable food excites the vomiting reflex and is rejected to protect the body from the absorption of injurious substances. Similarly, thoroughly comminuted, complete and properly proportioned food in the secondary digestive pouch, the proximal colon, is normally kneaded back and forth to promote complete digestion and absorption, but aliment not fulfilling these requirements is propelled onward rapidly and dejected. Such a propulsive action may seem inconsequential; but Howell writes, "the value of this reversal of movement of the bowels (antiperistalsis) at this particular point would seem to lie in the fact that it delays the passage of material toward the rectum, and by thoroughly mixing it gives increased opportunities for the completion of digestion and absorption" (9).

The sign of the normal operation of the proximal colon is the formation of the intestinal contents into uniform segments, which make up the normal feces; for Elliott and Barclay-Smith write, "a segment from its (the proximal colon) contents is every now and then nipped off by a ring of constriction, and carried away to be moulded in its further passage down the colon to the firm fecal nodule" (10). The passage of the colonic contents in man is brought about by two *different actions; one, evidently* the normal is that of Fischl and Porges (11) by which the contents of the proximal colon are moulded into segments that are passed slowly through the distal colon; the other, evidently the abnormal is that of Holzknecht (12), by which large irregular masses form in the caecum and are passed propulsively through the entire colon. This act procedures soft and formless feces. which in the practice of anabolic nutrition are a sign of intestinal indigestion and malnutrition.

The intestinal rate as another index of absorption in animals, has been shown by Gross (13) to exhibit marked variations according to the kinds of food ingested. In properly fed rats, charcoal takes 9 hours to appear in, and 120 hours to disappear from the feces; but in those without vitamin A the intestinal rate was 6 to 48 hours, and in those without vitamin B it was 16 to 384 hours. This abnormally slow rate is explained by the fact that animals in vitamin B deficiency lose their appetite and consume so little food, that their bodily needs are not fulfilled and at the same time enough passed on to produce normal dejections. The intestinal rate as an index of absorption in man, has been described by Burnett (14) to exhibit similar variations according to the kinds of food ingested and other factors. In adult patients who corrected their ways of eating to operate the proximal colon normally, one and sometimes two segmented stools are common daily, yet the marked evening meal takes about 63 hours to appear in, and 134 hours to disappear from the feces; and this rate is considered normal. On the other hand, in those who eat erroneously, the dejections are often irregular and the rate is frequently 14 to 63 hours. Such a rate is shown in Record 1, and in the practice of anabolic nutrition is applied as a sign of malabsorption, by which there is a failure in the final and most important phase of nutrition—assimilation.

Structural changes in the bone cells of scorbutic animals from a failure of assimilation have been described by Wolbach and Howe (15); for they state that "after seven to nine days of deficient diet there was an increase in the number of osteoblasts applied to the cartilage columns. . . From twelve to sixteen days . . . the osteoblasts migrated from their original positions and assumed the shapes of fibroblasts." Thus, when highly specialized cells do not receive normal nutrient substances from food, they revert to a lower and commoner type of cell. "But the administration of orange juice . . . was promptly followed by the deposition of bone matrix between the fibroblast-like cells." Thus the consumption of complete food and normal assimilation, produced a regeneration of the osteoblasts and the formation of normal bone.

This process appears similar to that produced in patients from malabsorption to cause metabolic diseases; for through a failure of normal nutrient substances to maintain a weak skin, joints, or some other tissue, in a healthy state, the cells break down in a recognized disease. And in these circumstances, the cause of the disease can only be removed by the production of normal nutrient substances to regenerate the cells, and this process is evidently brought about in patients by the correction of erroneous ways of eating and living to operate the nutritive apparatus normally, and to create anabolic or normal nutrition by which an exact and improved state of health can be *acquired and subsequently controlled.*

CONCLUSIONS

Health has been a vague and variable condition of the human body, but its maintenance and restoration have been more assured of late, from an understanding of the needs of the healthy body for complete food; and thus some of the established deficiency diseases have been relieved, cured, and prevented. Obviously eating too fast and too much, irregularly, disproportioned meals, or the frequest use of laxatives are not conducive to normal nutrition and health; but by regarding the digestive system as a perfect nutritive apparatus in which a function of the colon only oper-

ates from right eating to produce normal feces and normal intestinal rates, these erroneous ways of eating provoke a previously unrecognized kind of intestinal indigestion, malnutrition and disease. This is because the food consumed does not complete its cycle of digestion and absorption, and nourishment goes through instead of into the body. Thus, there is a failure in the final and most important phase of the nutritive processes—assimilation—and the exact and improved state of health from anabolic or normal nutrition, cannot be maintained. Principles for the creation and control of this state of health to cure disease, have been applied in the treatment of some of the skin diseases and arthritis; and patients who understood and carried out the principles, have been cured of these diseases.

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Studies on Constitution and Ulcer

III. Gastric Secretion in the Healthy Members of "Ulcer Families"*

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SINCE statistics disclose a high familial incidence of gastric and duodenal ulcer, the existence of an ulcer constitution, which in response to harmful stimuli might lead to this disease has been postulated by various authors (1).

Celsus, at the beginning of the Christian era, wrote that constitution may predispose to certain diseases; and Hunter, in the eighteenth century, discussed how constitution may prevent or facilitate the occurrence of disease (2). Many attempts have been made since then to define constitution, but no definition seems to be generally acceptable.

With respect to ulcer the tendency has consisted largely in an effort to express constitution either anthropometrically as a definite body build, usually asthenic (3), or on a functional basis. The "vagotonia" of Eppinger and Hess (4) and the "vasoneurotic" diathesis of Mueller (5) are illustrations of this thesis which have neither been proven nor accepted (6).

More recently, the concept of "organ diathesis" has been formulated, which tries to explain the tendency to ulcer formation in weakness of individual organs, *i.e.* the proximal gastro-intestinal tract.

Dr. Arthur Hurst (7) originally described the significance of variations in gastric physiology and anatomy occurring in normal, healthy adults. The extremes of these variations have been classified as hypersthenic and as hyposthenic stomachs, the former characterized by hyperchlorhydria, hypersecretion and a high, horizontal, hypertonic, rapidly emptying stomach, and the latter by hypochlorhydria, hyposecretion and an elongated, ptotic, slowly emptying stomach.

Both types of stomach usually are found to be associated with physical types of body build. The hypersthenic stomach with "hypersthenic," muscular, persons, and the hyposthenic stomach with "hyposthenic," slender persons with weak musculature. Both types of stomach are frequently familial, and, according to Hurst, both predispose to the occurrence of peptic ulcer. The hypersthenic individual is distinct from

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the vagotonic, because it lacks the symptoms of bradycardia, hyperidrosis, myosis, etc. The hypersthenic stomach frequently contains free acid in the fasting state. Its tendency to hyperacidity renders it prone to harmful effects of alcohol, smoking, etc. The tendency of the hyposthenic stomach to hypochlorhydria diminishes the bactericidal properties of this organ and

TABLE I

Relationship between ulcer patients and normal subjects tested

Relationship	Number
Father-son	21
Mother-son	9
Father-daughter	26
Mother-daughter	5
Brother-brother	6
Sister-brother	1
Brother-sister	8
Uncle-nephew	2
Son-father	1
Son-mother	2
Cousin	1
Total	82

thus, according to Hurst, facilitates the development of a gastritis or duodenitis which may lead to ulcer. The observations of Hurst have, however, been contradicted (8).

It has been our experience, that one or more members of the family of a patient with gastric or duodenal ulcer soon or late developed this disease and therefore our attention was drawn toward these families as potential sources of future gastro-intestinal pathology. It was assumed that the healthy members of these families would have some abnormality in gastric function that might predispose them to the occurrence of ulcer. We therefore undertook a study of the gastric secretion in the normal asymptomatic members of the families of ulcer patients.

METHODS AND PROCEDURE

The present work presents a statistical analysis of gastric secretion in the relatives of ulcer patients. All were healthy, few had slight gastro-intestinal complaints, as anyone may have from time to time, none presented an anamnesis indicating ulcer, and none had consulted a physician for gastro-intestinal complaints. Table I presents the variety of relationship occurring in the series. Forty-one females and 41 males from 54 families, with an age range between 8 and 64 years are represented.

Gastric secretion was obtained by Rehfuss tube. The residue of the fasting stomach was aspirated, measured and titrated. At ten minute intervals, two more aspirations were made, the specimen measured, 10 c.c. retained for titration, and the remainder returned. These latter values represent basal secretion. The test meal was now provided. It consisted of 8 arrowroot cookies and 400 c.c. water (9). After one hour, the stomach was emptied completely, the contents measured, a 10 c.c. specimen retained for titration, and the balance returned. One-half or one hour later, the final aspiration and measurement were made. The results of titration were expressed in clinical units.

The data accumulated in this manner have been statistically analyzed in accordance with the technique presented by Vanzant, Alvarez, Berkson and Eusterman (9). This method made possible a comparison between the present group and the normal standards of secretion accumulated from nearly 4000 subjects. The comparison is expressed as the mean difference in clinical units between the values found and the normal standard, plus or minus the probable error. The cases lacking free acid following the test meal have been calculated separately, the percentage incidence of achlorhydria in each age group being compared with the normal incidence of anacidity for that classification. The values for free and combined acidity used in calculation are those obtained one hour after the test meal. The later aspiration subserved to differentiate between true and apparent achlorhydria. The former indicates the absence of free acid in all three specimens after the test meal, the latter indicates the absence of free acid in the one hour specimen but its appearance one-half or one hour later. Histamine was never employed in order to preserve identity with the experimental conditions of the standards employed.

RESULTS

Table II summarizes the number of subjects, the average volume and the free and total acidity in response to the test meal, the characteristics of the fasting residue, and the incidence of achlorhydria for each age group.

As is evident in Table III*, the healthy members of ulcer families, both male and female, present a distinctly lower free acid response to the stimulus of an Ewald meal than does a normal group. The males further reveal a statistically significant comparative depression in total acidity, and a suggestively significant relative augmentation in volume. The changes in total acidity and volume are not significant among the females.

Achlorhydria is more frequent among females, and no male in the age range of 15-64 years exhibited absence of free acid. However, the percentage incidence of achlorhydria for the female ulcer relatives is actually lower than the normal prevalence of anacidity (9).

Vanzant, *et al*, have not reported the incidence of anacidity below the age of twenty years. However, extrapolation of their data would indicate that the young members of ulcer families demonstrate a high incidence of achlorhydria. Muhl (10) and Klumpp and Neale (11) report no instance of achlorhydria in a total of 120 normal children. Yet Wright found that 4% of 230 children were devoid of free acid (12).

Finally the fasting residue of the ulcer relatives deviates from normal, tending frequently to be of the same degree of acidity as the specimen taken one hour after the test meal (see Table II).

COMMENT

In a general way, the above data demonstrate the existence of significant secretory deviations from normal in the seemingly healthy members of ulcer

*The values for total acidity and volume in Table III do not include the results from the younger groups up to 20 years of age because no comparable statistical material of a normal population of that age group is existing (see 9).

TABLE II

Gastric secretion of normal relatives of ulcer patients

		Residue			Ewald Meal				
								Achlorhydria	
Age Group	No. of Subjects	Vol. c.c.	Free Acid	Total Acid	Vol. c.c.	Free Acid	Total Acid	Apparent	True
Males	41							(Number of Persons)	
10-14	5	35	42.0	55.0	168	45.0	65.0	2	1
15-19	20	54	28.5	47.4	132	26.8	53.8		
20-24	9	58	27.1	43.1	124	33.0	60.0		
25-29	4	60	24.0	43.0	120	31.5	52.3		
30-34	1	50	10.0	25.0	125	30.0	61.0		
45-49	1	30	5.0	25.0	125	20.0	46.0		
60-64	1	30	0	10.0	100	15.0	36.0		
Females	41								
8	1							1	
10-14	4	43	30.7	54.0	99	22.0	52.7		1
15-19	18	58	22.2	41.9	118	24.3	50.2		
20-24	8	31.7	14.2	31.2	99	19.5	46.0	1	1
25-29	4	69.0	13.8	34.0	106	20.0	46.5		
30-34	1							1	
35-39	1	10	0	10.0	110	25.0	51.0		
45-49	1	20	20.0	41.0	80	16.0	34.0		
50-54	1	45	5.0	25.0	15	20.0	51.0		
55-59	1	35	15.0	30.0	80	36.0	66.0		
60	1								1

families, the male deviations exceeding the female.

Whether or not these variations can be legitimately interpreted as representing a tendency to ulcer formation still remains questionable. In the course of the three years of this study three subjects, asymptomatic at the time of the test, ultimately developed clinically demonstrable ulcers.

The diminished acidity of the relatives of ulcer patients may result, as Hurst supposed, in a lowered antiseptic barrier with ultimate gastritis and ulceration. This theory may explain the pathogenesis of gastritis or of acute ulcers much more than it does that of the chronic ulcer.

Another possibility is that hypoacidity may merely be one of the symptoms of a more fundamental pathology, as yet unknown, which, independent of secretory changes, is capable of inducing ulcer. The presence of rather high acidity in the resting stomach, similar to that of ulcer patients, also points in that direction. If one considers the healthy members of ulcer families as potential ulcer patients, and if one accepts the statistical validity of the hypoacid response to an Ewald meal, of this group, one must assume that the hyperacidity in cases of duodenal ulcer is preceded by hypoacidity, and that hyperacidity may be caused by an unknown factor or by the ulcer and not *vice versa* as is generally believed.

TABLE III

Average difference in gastric secretion between healthy ulcer relatives and normal population

	Males	Females
Free Acidity	— 18.1 ± 1.834	— 9.6 ± 1.686
Total Acidity	— 8.8 ± 2.832	— 5.4 ± 2.610
Volume c.c.	— 7.3 ± 2.617	— 5.3 ± 2.207

It is important to emphasize that the members of ulcer families represent potential ulcer patients, so that if the incidence of ulcer is to be curtailed, in the absence of specific therapy, adequate prophylaxis should be directed toward protection of these vulnerable individuals.

While it is not within the scope of this paper to discuss in detail the prophylaxis of ulcer, our present studies suggests the advisability of such simple precautions as the following: In view of the low acidity which we found to be prevalent in this family group, attention to oral hygiene and the removal of infectious foci should be stressed, as this may prevent bacterial invasion of the stomach and its sequela.

In view of the fact that mental and physical overstress, and particularly social and sexual maladjustments are important as ideological factors in the genesis of the ulcer syndrome, correction of these

should be attempted particularly in the healthy members of ulcer families.

SUMMARY

While it is known that ulcer "runs" in families, nothing has been known about gastric functions of the healthy members of such families, which have to be considered as potential ulcer patients. Therefore, the gastric function was tested in 82 healthy relatives of ulcer patients, not having stomach or intestinal complaints. The response of this group to an Ewald meal revealed too low values for free acidity in both males and females and the presence of much free acid in the resting stomachs of a great number of them. The abnormal response to the Ewald meal and possibly also the high acidity of the resting stomach may be interpreted as predisposing to gastritis. It may be the expression, however, of an abnormal gastric mechanism, so far unknown, which may produce both, abnormal secretion and ulcer. Dietary, hygienic, and social adjustment as prophylaxis for ulcer is advocated among the healthy members of ulcer families.

Note: We gratefully acknowledge the help of our Social Service Department through Miss Eleanor Scher.

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SECTION II—*Experimental Physiology*

Nocturnal and Diurnal Variations in the Acidity of the Spontaneous Secretion of Gastric Juice*

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THE views have been prevalent concerning the secretory activity of the empty stomach. Beaumont (1847) observed that gastric juice was never found free in the unstimulated stomach of Alexis St. Martin, and Pavlov (1910) noted that in the absence of psychic disturbances or food, the gastric glands of the dog likewise remained quiescent. Carlson (1916) subsequently presented evidence in support of a more or less continuous secretion in the absence of food or psychic factors as a normal phenomenon in both animals and man. Divergence of opinion has persisted. Much of the substantiating evidence has been indirect. Rehfuss and Hawk (1921) inferred the character of interdigestive gastric behavior from a study of the fasting residuum aspirated preceding the administration of a test meal. Crohn and Reiss (1917) had already reported that an "after secretion" might persist for many hours post-prandial. They considered it a manifestation of pathological hypersecretion. In a careful series of physiological studies, Lim (1924) looked upon the juice secreted in the absence of all intentional and avoidable stimuli as a "basal secretion" to which the subsequent enhanced activity of the glands as a result of controlled stimulation must be related. It was not until 1926 that Galambos suggested the periodic aspiration of the fasting stomach as a feasible clinical diagnostic method. In 1931 Polland and Bloomfield made a systematic study of this basal secretion and also suggested that herein might lie a new function

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TABLE I

The mean free and total acidity of the gastric juice spontaneously secreted day and night

	Night		Day	
Subject	HCl	T. A.	HCl	T. A.
	c.c. N/10 NaOH to neutralize 100 c.c. gastric juice			
F. H.	61.28	93.56	37.48	66.80
A. C.	49.20	59.62	42.93	49.31
H. G.	42.62	70.95	29.56	56.12
R. C.	41.91	45.08	37.07	41.60
R. W.	31.33	37.76	22.81	27.50
A. D.	25.07	27.13	18.69	27.93
D. K.	19.17	25.29	10.93	17.93
A. L.	16.94	22.52	26.62	32.31
E. W.	13.71	41.38	16.12	44.16
K. S.	11.66	16.66	15.56	19.93
L. E.	2.20	29.65	7.00	30.39

test of first importance in the clinical assay of the secretory capacity of the gastric mucosa. The whole problem has been recently reviewed by Babkin (1932). He believes there can be no further denial of the "secretion of a regular gastric juice by fasting man," and advances the view that such secretion is always due to the action of normal or abnormal stimuli, the glands remaining at rest or active according to whether these stimuli are present or absent.

The observations cited have been limited to a relatively few hours of either continuous or periodic aspiration. The only long time studies of the continuous secretion of the fasting stomach are those concerned with the determination of gastric secretory activity during sleep at night. Chalfen (1928), Henning and Norpoth (1932, 1933) and Winkelstein

TABLE II

The highest free and total acidity of the gastric juice spontaneously secreted during the day and night

	Night		Day	
Subject	HCl	T. A.	HCl	T. A.
	c.c. N/10 NaOH to neutralize 100 c.c. gastric juice			
F. H.	73	110	63	90
A. C.	82	88	62	68
H. G.	70	102	51	77
R. C.	92	94	51	58
R. W.	63	71	42	46
A. D.	76	81	46	50
D. K.	30	46	32	38
A. L.	42	48	42	51
E. W.	59	89	33	66
K. S.	28	35	34	40
L. E.	17	48	23	52
Average	58.8	73.8	43.8	57.8

(1935) report that secretory rest characterizes the nocturnal response of normal subjects in contradistinction to the elaboration of a juice of high acid value by patients suffering from peptic or duodenal ulcer. The object of our study was to extend day time observations to comparable periods and to contrast the diurnal and nocturnal response of the same subject.

METHODS

All observations were made upon young adult university women free from gastric symptoms or disease. Day time studies commenced 15 hours after the last meal. Fluids were forced on the preceding day, to ob-

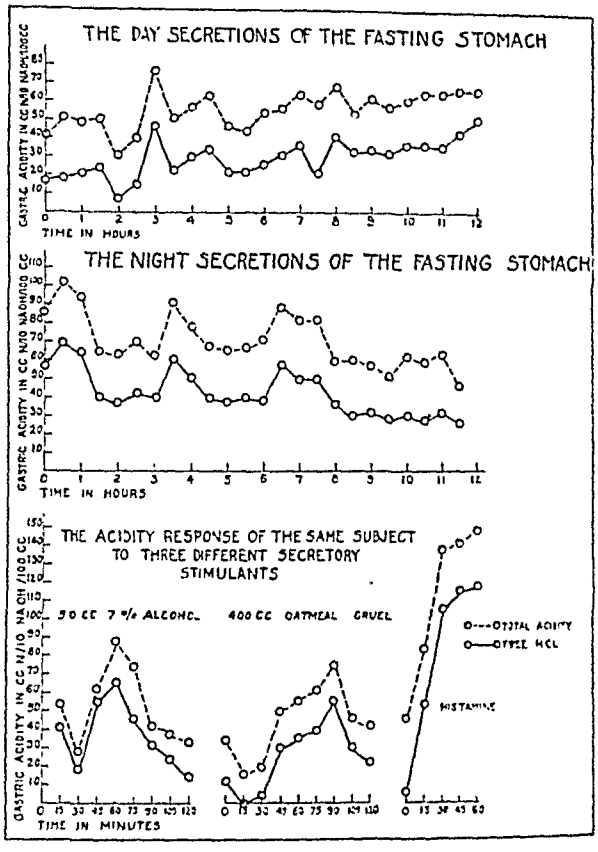


Fig. 1. A comparative study of the acidity of the spontaneous day and night secretion of the fasting stomach of a subject responding well to histamine, .1 mg./10 kilo, and to routine test meals of gruel and alcohol. Note that the scale of times referred to the axis of abscissas in the short experiments is double that of the 12 hour observations.

tain maximal hydration and thus allay the discomfort of abstinence and combat the aspiration of fluids. On the day before nocturnal observations the usual breakfast was eaten, avoiding only meats and fried foods. Luncheon consisted solely of nutritious liquids. Dinner was omitted. Fluids were stopped within three hours of the experiment, since Rehfuss and his coworkers had found that water alone might act as a secretory stimulant (1914).

The technique of intubation was learned prior to the use of any individual as a subject. The Rehfuss tube was modified by attachment of the metal olive to 1 16 by 1 32 or 3 32 by 1/32 Dakin's tubing. This was voluntarily swallowed without artificial lubrication or the ingestion of fluids, and was well tolerated for

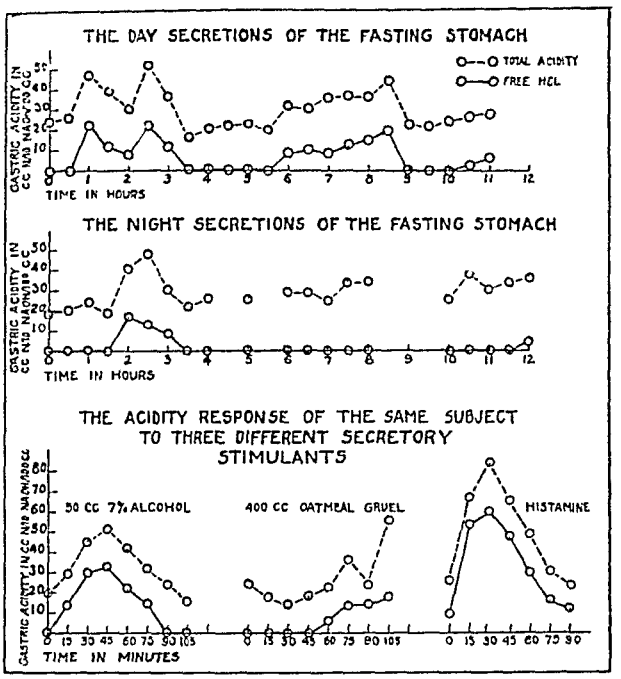


Fig. 2. A comparative study of the acidity of the spontaneous day and night secretion of the fasting stomach of a subject responding poorly to gruel, and only moderately to alcohol and histamine stimulation. The scale of times referred to the axis of abscissas in the short experiments is double that of the 12 hour observations.

many hours. The heavy end of the tube was allowed to seek the lowest pole of the stomach. Before assuming recumbency at night, the correct tube position was determined with the subject in the sitting posture, after which fixation was attained by the application of adhesive plaster. All nocturnal observations were made with the subject sleeping in the laboratory, from 7 to 10 of the night hours being spent in bed. Day time experiments were performed with the subject up and about, occupied with quiet sedentary work. Saliva was not expectorated. A small sample of the gastric contents was aspirated with a syringe half hourly, first mixing the fluid which had accumulated in the stomach. Chemical analyses were performed immediately after the withdrawal of gastric juice, both day and night. Visible mucus was removed by centrifugal separation. The supernatant gastric juice was decanted and free and total acidity were determined by titrating with .1 N NaOH, using a micro burette, fitted as described by Hollander (1931) with a hypodermic needle. During the early experiments Töpfer's reagent and phenolphthalein were used to determine end points for free and total acidity respectively. Subsequently bromphenol blue and phenol red were substituted. The presence of bile was noted and its quantity estimated by subjective evaluation of the color of the freshly drawn sample. Blood was detected by the benzidine test. When positive in repeated aspirations the experiment was terminated.

The procedure is open to criticism because of contamination of the gastric secretion by saliva, pyloric escape of gastric contents, reflux from the duodenum, and the unknown influence of the residue of preceding glandular activity upon the acid value of succeeding samples. To perform a long time experiment under the most ideal conditions the following modification of procedure was adopted in one case. Observations were commenced after a 22 hour fast, to rid the upper alimentary tract of food. The subject remained in a semi-recumbent position in bed during 17 consecutive hours of observation. Saliva was continuously removed by suction. The gastric contents were continuously aspirated by the application of a constant gentle negative pressure, using the intestinal decompression method of Wangensteen (1933). A liter and a half of gastric juice was withdrawn. To combat the dehydration and hypochlorema which accompany the total loss of gastric secretion (Dragstedt and Ellis, 1930) 1400 c.c. of warm physiological saline were introduced by hypodermoclysis between the 6th and 11th hours of observation.

RESULTS

In a series of 55 preliminary experiments on 6 normal young adult women we confirmed the presence of a continuous secretion in the fasting stomach over periods varying from 1 to 6 hours. A total of 34 long time experiments were then performed, 21 during the night and 12 during the day, on 18 and 11 subjects respectively. Seven of the day and 3 of the night ob-

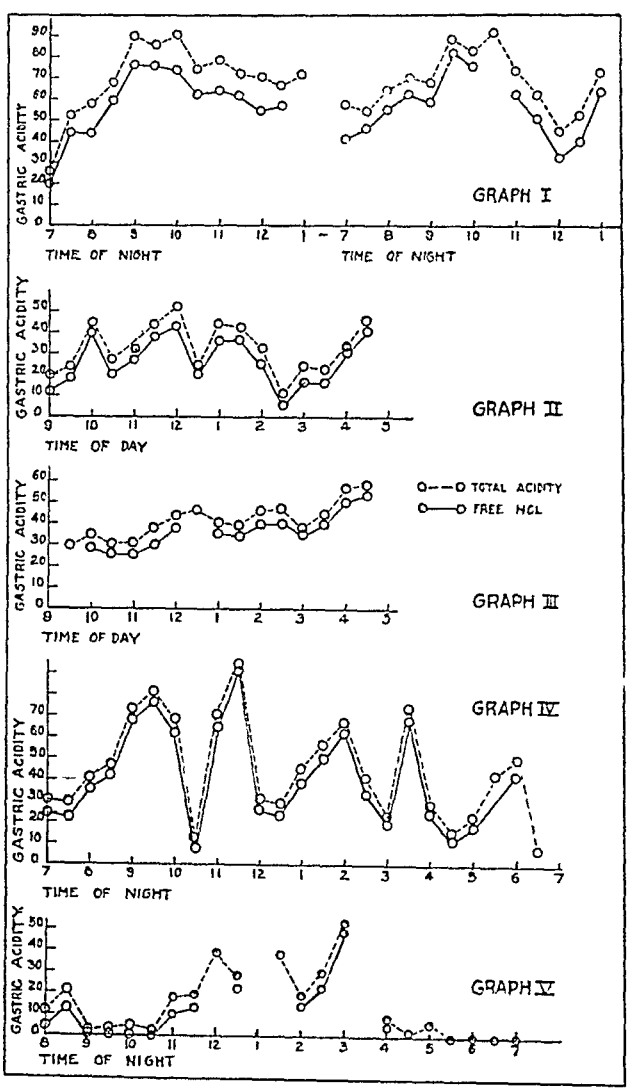


Fig. 3. Illustrative graphic records showing the continuous secretion of the fasting stomach and the periodicity of its acid response in the absence of intentional stimulation.

servations were limited to 8 consecutive hours. The remaining 20 were 12 hours in duration. One extended over 17 hours and thus involved day and night aspiration. Eleven subjects submitted to both diurnal and nocturnal observations.

The juice aspirated was often of high acid value and not infrequently exceeded in acidity that produced in response to a test meal. Figure 1 illustrates the acidity of the gastric juice withdrawn from both the stimulated and spontaneously secreting stomach. The glandular activity of the fasting stomach was sufficiently continuous to yield samples of gastric juice at half hour intervals, day and night. The distinct periodicity in the intensity of the reaction makes the contours of the spontaneous acidity curves indistinguishable from those induced by deliberate stimulation.

The behavior of the empty stomach and the functional capacity of the mucosal acid producing cells as revealed by test meals or histamine stimulation seem to be related. This is evident in the comparison of Figures 1 and 2. So low was the secretory rate in the latter experiments that adequate samples were obtained from the fasting stomach with difficulty and occasionally no juice could be withdrawn. There is a uniformity in the pattern and level of the response, night, day, and after stimulation.

In general, the acidity of the gastric juice spontaneously liberated during sleep at night was *higher* than that produced in the day time. Table I presents the individual average free and total acidity of the night and day secretion of 11 subjects. By arranging these in order of the titration value of the nocturnal free HCl, the mean day secretion exceeds the night in potency only in those cases in which the functional capacity of the mucosa is lowest. If the stomach has the ability to liberate spontaneously a juice of high acid value, its nocturnal responsiveness exceeds that of the day. This is more evident in Table II, in which are presented the single highest day and night free and total acidity values. The mean highest acidities for the group as a whole were 58.8 for free HCl during the night and 73.81 for total acidity, in contrast to 43.8 and 57.8 during the day.

Graph I of Figure 3 shows the similarity of the gastric behavior of one subject on two different nights. The acidity is high and the response is cyclic. The periodic character of the reaction is typically illustrated in Graph II. The greatest suppression of the day in contrast to the night secretion of a single subject, is reproduced in Graph III and IV. This subject slept well and uninterruptedly throughout the major portion of the night, precluding psychic stimulation of external origin. On the contrary the subjects whose acidity response is reproduced in Graph V, slept fitfully and spent a restless and uncomfortable night in the laboratory.

Continuous aspiration of the gastric contents did not affect the appearance of recurrent waves of rising acidity (Figure 4). The findings were identical with those yielded by periodic sampling. The acidity was highest during the night. Toward morning it dropped abruptly until no free HCl was detected in the aspirated gastric contents. Subsequently it rose again. The period of maximal acidity coincided with the interval of saline administration. Fluid lost by gastric aspiration was roughly compensated for by injection, but absorption from the subcutaneous tissues was incomplete when the experiment was terminated 6 hours after the cessation of hypodermoclysis. At the end of 17 hours there was no sign of secretory exhaustion.

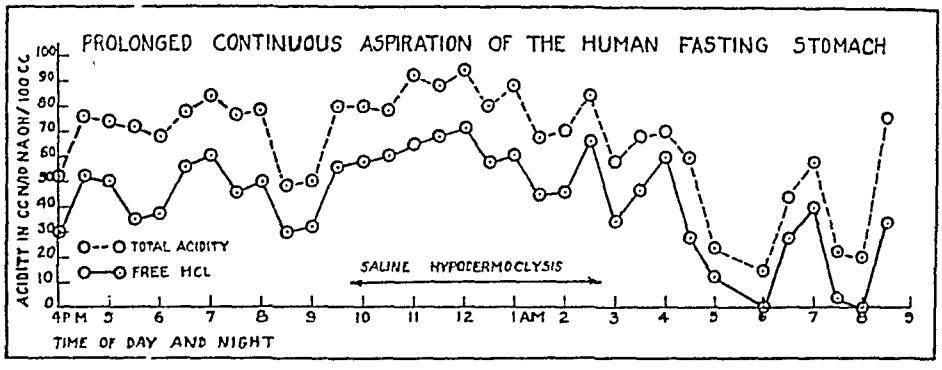


Fig. 4. Nocturnal and diurnal variations in the acidity of the spontaneous secretion of gastric juice, continuously collected for 17 consecutive hours by the decompression method of Wangensteen. Fluid loss was partially compensated by saline hypodemoclysis.

Bile was almost continuously present in the samples withdrawn from the fasting stomach. Regurgitation as evidenced by fluctuations in the intensity of the color of the aspirated samples was inconstantly related to depressions in acidity. When the secretion rate was low the benzidine test was most frequently positive for occult blood. We had already called attention to the difficulty of obtaining blood free samples from the fasting stomach on double intubation (Hellebrandt, 1935). It suggests that the metal olive of the Rehfuss tube may traumatize the mucosa when unbuffered by a fluid test meal, especially during vigorous peristalsis. The use of a thin, weighted, perforated rubber tube did not completely abolish this finding. Trauma by intubation aspiration may be more common than is supposed. This negates the value of aspiration of the fasting stomach as a practical clinical test. Except for transitory discomfort, our subjects showed no ill effects from the procedure. Milk was administered immediately after the withdrawal of the

tube, and a bland, easily digestible meal was served before discharge from laboratory.

DISCUSSION

If the parietal cells put out a juice of constant acidity and this is elaborated continuously, we can ascribe the spontaneous variations in the titration values of aspirated samples to several mechanisms. There is ample opportunity for contamination with extra-gastric secretions, of which we have partially eliminated only saliva as a contributory acidity depressant. In the absence of quantitative data it is impossible to evaluate the importance of duodenal regurgitation. The purest gastric juice is a mixture of the secretions of a variety of cells, susceptible to selective stimulation and unequal activity (Hollander, 1931; Vinsberg and Babkin, 1931). Carlson (1916) had suggested that the stimulus for the continuous secretion of the empty stomach may reside in the autodigestion of constituents normally present in the gastric juice. Continuous aspiration affords minimal opportunity for stimulation by this route, yet periodicity in the level of the response remains as evident as that characteristic of a stomach from which small samples of the contents are only intermittently removed. That the mechanism is a humoral one emanating from the intestine seems improbable. It would be difficult to explain the cyclic nature of its release.

Chalfen (1928) suggested that the secretion of the fasting stomach was a conditioned reflex, since in his experience the exclusion of psychic stimuli by sleep was associated with a secretory depression. This is not in agreement with our findings. Further, the day oscillations in our experiments display no peak acidities coincident with the habitual time of eating. Henning and Norpoth (1932) also considered the fasting secretion a psychoreflex. Like Chalfen, they find the abolition of secretion characteristic of sleep. In their experiments, the "waking state" was associated with a prompt elevation in the acid level of the juice aspirated from the stomach. Inability to sleep comfortably under laboratory conditions was never accompanied by the production of a juice of high acid value in our experiments. The maximal acidities were obtained from subjects whose sleep was least affected by the unavoidable disturbances incidental to the procedure.

The largest series of normal subjects showing low or absent free HCl during sleep at night is that of Winkelstein (1935). However, aspirations were commenced by him only 2½ hours after a full dinner, and although food fragments were present for 4 hours thereafter, the quantity of secretion was small, "seldom exceeding 15 c.c. in the whole night," and 40 per cent of the normal subjects showed no free HCl. Babkin (1932) had reported that food residues, even when present in insignificant amounts, exert a stimulating effect on the secretion of gastric juice. Digestion must have been at its height when Winkelstein's experiments were commenced. Carlson (1915) estimated that 700 c.c. of gastric juice were produced by a normal man in response to an average meal. In our long time experiment, the mucosa elaborated a juice of high average acidity at a mean rate of 14.7 c.c. 10 min. for 17 consecutive hours without evidence of secretory exhaustion. It is difficult to reconcile these observations with the findings of Winkelstein.

Carlson (1916) demonstrated that gastric hunger contractions are augmented during sleep. Subsequently (1923) referring to the heightened secretion observed by Luckhardt and Johnston (1924) in hypnotic sleep, he predicted that an augmentation of gastric gland activity would probably also be found to occur during natural sleep at night, the secretory and motor mechanisms of the stomach being similarly governed. Our findings substantiate this prediction. Gastric secretion, like gastric motility, is augmented during sleep at night. Both are characterized by irregularly recurrent periods of activity and relative quiescence. We have already postulated a secretory-motor relationship in the fasting stomach of man (Hellebrandt, 1935), acidity and motility varying in unison. The demonstration of fluctuations in the acidity of the fasting secretion, day and night, adds weight to this hypothesis.

CONCLUSIONS

1. The normal fasting stomach secretes continuously, day and night.

2. The fasting gastric contents may exceed in acidity that accumulated in response to test meal stimulation.

3. The acidity of the fasting secretion rises and falls intermittently, in the absence of all intentional stimulation.

4. The mean acidity of the night secretion of the fasting stomach exceeds that of the day secretion.

5. A secretory-motor relationship is postulated to explain the fluctuation of the acid values of the aspirated gastric contents though there is no quantitative evidence to exclude extra-gastric contamination as the modus operandi.

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On the Inhibitory Effect of Corpus Luteum on Gastric Secretion*

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IT has been noticed in this laboratory that pregnant bitches do not respond normally to secretion and histamine stimulation of gastric secretory activity. Strauss and Castle (1, 2) have presented evidence showing that pregnant women usually show a tendency toward achlorhydria. The possibility that one of the hormones elaborated in the ovary during pregnancy exerts this inhibitory effect was investigated.

METHODS

Pinky, the animal used in this work, is a young healthy adult male dog who had an ileo-gastrostomy performed in November, 1935. He is normal in all other respects. Before each experiment food was withheld for 12 to 36 hours. The dog was trained to lie quietly during the experiment. Through the fistula, a rubber tube was introduced on the end of which was a light rubber balloon. The other end of the tube was connected to a chloroform manometer whose float recorded pressure variations on a smoked drum. A catheter with the closed end perforated by a number of openings was also inserted through the fistula. The outer end of the catheter was kept closed with a clamp between operations. At five minute intervals the clamp was removed, the gastric contents aspirated and 50 c.c. of tap water were introduced. Ten c.c. portions of the aspirated gastric content were titrated with N/40 NaOH to determine free and total acid. Töpfer's reagent and phenolphthalien were used as indicators. The titration values of the gastric contents gave information about the relative amount of secretion (at least of hydrochloric acid) during the five minute period the sample was in the stomach.

EXPERIMENTAL

Control experiments were run using 2 mg. pilocarpine HCl as a stimulant. This resulted in a greatly increased flow of gastric juice with a high acidity and a high mucus content. Peptic activity was not determined. The results of a typical experiment are shown in Table I.

We feel that the course of gastric secretion may be followed best by the free acid values because of the buffering effect exerted by the varying amounts of saliva and mucus in the various samples. Results of a typical experiment using pilocarpine HCl show that the maximum acidity is reached about 37 minutes after stimulation, although high values are reached within 25 minutes and are maintained for at least 40 minutes.

After control experiments were done the animal was put on a course of corpus luteum (Lilly). It was given one ampoule a day (each ampoule represents 3 grains dessicated corpus luteum) for 13 days. At the end of this time the effect of pilocarpine was again determined. The animal was given 2 mg. pilocarpine HCl accompanied by 1 c.c. corpus luteum. Results of this experiment are given under Experiment I in the Table. The acid values in this experiment did not rise so high as in the control experiment. One hour and four minutes after stimulation, the acidity began to increase. This experiment seems to show some inhibition of pilocarpine stimulation by corpus luteum. As the effect of corpus luteum in this experiment seemed to be slight, another experiment was performed, the animal being given 2 mg. pilocarpine accompanied by 2 c.c. of corpus luteum, followed in one-half hour by another 2 c.c. dose. The results of this experiment are given in Experiment II in the Table. This experiment shows no inhibition by corpus luteum of the secretion induced by pilocarpine. Corpus luteum also apparently had no effect upon the gastric motility. In the second experiment, the peak of acidity was reached 48 minutes after stimulation and the acid values were of the same order as those obtained when pilocarpine alone was given. High acid values were still present when the experiment was discontinued one hour after pilocarpine stimulation.

TABLE I

Time	Control Free Ac.	Control Total Ac.	Experiment I Free Ac.	Experiment I Total Ac.	Experiment II Free Ac.	Experiment II Total Ac.
00	0.6	1.1	0.4	1.0	0.0	1.2
05	1.1	1.9	0.1	1.4	0.6	2.3
10	0.5	1.7	0.4	3.0	3.0	5.0
15	5.0	6.0	3.3	4.1	3.7	6.6
20	7.8	9.0	0.6	2.7	3.7	8.0
25	6.7	8.6	0.5	3.3	5.5	11.5
30	0.0	2.4	2.1	3.7	6.3	12.8
35	8.0	9.0	2.1	3.6	4.8	9.8
40	8.3	10.5	4.0	5.6	4.5	9.0
45	5.8	7.6	4.2	6.0	6.9	11.4
50	5.1	6.9	4.4	5.5	7.5	12.8
55	6.1	7.6	4.8	6.5	6.8	11.8
60	7.0	9.5	5.1	6.6	6.8	11.3
65			6.0	7.5		
70			4.5	6.0		

Free and total acid values are expressed as c.c. N/40 HCl.
In Experiment I, 2 mg. pilocarpine and 1 c.c. corpus luteum were given.
In Experiment II, 2 mg. pilocarpine and 2 c.c. corpus luteum were given followed by 2 c.c. corpus luteum one-half hour later.
Time is expressed in minutes from pilocarpine stimulation. 00 minutes is the time the pilocarpine was given.

DISCUSSION

Strauss and Castle state that the greatest decline in gastric acidity occurs during the second trimester of pregnancy with a rise during the last month to the level observed in the third month. As the corpus luteum involutes about the start of the eighth month of pregnancy, it was thought that perhaps the corpus luteum hormone might be the responsible agent. The doses of corpus luteum used in these experiments were probably physiologically adequate.

Since corpus luteum, in the dosage used, has no power of inhibiting the gastric secretory response to pilocarpine and since the animal produced acid just as efficiently after the course of corpus luteum as before, we conclude that the corpus luteum used does not contain the agent responsible for the diminished gastric acidity of pregnancy.

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SECTION III—*Nutrition*

Experimental Gout in Turkeys*

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THE major portion of the uric acid excreted by birds is derived from the conversion of urea in ordinary protein metabolism. Administration of urea increases the excretion of uric acid by normal birds. Minkowski demonstrated that the synthesis of uric acid from urea occurred in the livers of birds since such synthesis did not occur if birds were hepatectomized. Von Mach (2), after repeating these experiments, pointed out that uric acid did not entirely disappear from the urine of hepatectomized birds owing to the two sources of uric acid in these animals, one by synthesis from urea, which process occurs only in the liver, and the other from the purine bases liberated by nuclear metabolism throughout the body; the latter is independent of the action of the liver.

Urea is not converted to uric acid by animals other than birds and reptiles. Other animals, including man, possess a mechanism for the destruction of uric acid which varies in efficiency in the various species. The liver is also responsible for the destruction of uric acid (3). The normal dog excretes only traces of uric acid, but after removal of the liver large amounts of uric acid are found in the urine and no evidence of destruction of uric acid can be demonstrated. Because of the ability of animals to destroy uric acid this substance does not increase beyond a certain level in the blood of animals with complete urinary retention.

Urinary retention by birds produces a rapid, marked increase in the uric acid content of the blood and little elevation of the concentration of blood urea. Uremia is indicated by high levels of uric acid in the blood; values from 150 to 400 mg. per cent have been obtained (4). Under these circumstances there occurs a deposition of white, crystalline urates on all of the visceral surfaces and on the fascia of the muscles; deposits are also found on the articular surfaces of the joints (5, 6). The term "visceral gout" often has been applied to this condition and probably has led to some confusion in the literature. Until there is proof that uremia and tophaceous gout of birds are similar conditions we feel that the term "gout" should be reserved for the condition characterized by definite tophi.

Spontaneous avian gout is not infrequent among captive birds of zoölogical gardens. According to Fox (7), it occurs most often among parrots, gallinaceous and accipitrine birds, and herons. It has also been reported to have occurred among domestic birds such as the chicken, duck, goose and turkey. Kaupp (8) observed gout in a flock of capons. Kionka (9) experimentally produced gout in hens which he maintained exclusively on a diet of fat-free horse flesh. Gout became apparent in periods of from three to fifteen months. The symptoms and physical characteristics of this disease were similar to those of spontaneously occurring gout.

METHODS

One set of experiments was begun January 10, 1934, with eighteen turkeys which were at that time seven months old. They were placed, two each, in nine pens. Four pens were small cages measuring 26 by 26 inches, within an unheated building, and the remaining five pens were outside runs affording ample opportunity for exercise and a slightly greater range of temperature. Five combinations of diet were fed to these turkeys. The birds in outside pens and inside cages, which received identical paired diets, had free access to their food at all times. All turkeys received a basic diet of a commercial turkey mash containing wheat bran, middlings, yellow corn meal, meat and bone scraps, ground barley, soybean oil meal, ground oats, alfalfa meal, dried skimmed milk, dried buttermilk, limestone, salt, and cod liver oil. This diet contained 20 per cent protein, 4 per cent fat and 45 per cent carbohydrate. The five diets used were as follows: (1) the turkey mash without any additions, (2) turkey mash mixed with equal quantities of ground raw horse flesh, (3) turkey mash mixed with 5 per cent of crystalline urea, (4) turkey mash with a few leaves of fresh green spinach, and (5) turkey mash and cracker meal in equal quantities. Two birds were changed to diet 2 after having had diet 1 for eighteen weeks, and one bird was changed to diet 1 after having had diet 3 for twenty-six weeks.

All turkeys were weighed at approximately the same hour each week. At this time we also procured 1 c.c. of blood from the wing vein of each turkey. Determinations of the blood uric acid were made after proper dilutions, by the method of Folin (10).

On October 2, 1934, twenty other turkeys were placed in outside runs and given a diet composed of equal parts of turkey mash and ground raw horse meat. Four birds of the twenty were given intramuscular injections, three times each week, of 1 c.c. of a solution of uranium acetate containing 25 mg. of uranium. Four other birds of the twenty similarly received injections of solution of lead acetate containing 10 mg. of lead. Still four other birds of the twenty were fed cinchophen mixed with the food so

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that each turkey of the four received approximately 1 gm. of cinchophen each day.

Necropsy was performed on each of the thirty-eight birds; some died during the course of the experiments, but most survived the entire period. No pathologic changes were found in the visceral organs of any birds except those found associated with enterohepatitis. The lesions that were considered as gout consisted of tophaceous nodules about the feet, knees, or wings, and the depositions of chalky white material in the articular surfaces of the joints of the extremities. In examination of most of the gouty birds all of these changes were found, but in examination of a few the joints of the feet only were involved. Microscopic examination of the material from the gouty deposits revealed numerous needle-like crystals.

TABLE I

Effect of diet on blood uric acid

Additions to turkey mash diet	Bird	Location	Blood uric acid, milligrams per cent			Duration, weeks	Tophaceous gout
			Average	High	Low		
None	1	Pen	6.3	8.9	3.2	18	0
	2	Pen	6.2	10.9	2.6	18	0
	3	Cage	6.4	12.8	3.3	33	0
	4	Cage	6.9	14.2	4.1	33	0
	9	Pen	6.6	8.2	4.6	8	0
Horse meat 50 per cent	1	Pen	12.9	19.2	3.4	17	0
	2	Pen	12.2	17.8	6.1	17	0
	5	Pen	13.9	23.6	7.6	25	++
	6	Pen	9.3	18.6	5.0	20	0
	7	Cage	10.0	16.0	5.2	25	0
	8	Cage	7.3	14.8	4.3	31	0
Urea 5 per cent	9	Pen	8.0	10.6	4.4	26	0
	10	Pen	7.2	9.8	3.7	14	0
	11	Cage	6.5	11.0	3.4	31	0
	12	Cage	13.7	22.2	8.2	28	++
Green leaves	13	Pen	5.8	11.1	2.1	31	0
	14	Pen	5.9	7.8	3.2	18	0
	15	Cage	4.4	11.3	3.0	33	0
	16	Cage	5.4	9.4	3.0	33	0
Cracker meal 50 per cent	17	Pen	5.7	10.9	2.4	18	0
	18	Pen	4.6	6.7	2.1	18	0

RESULTS

The results of these experiments were summarized in Tables I and II from which most of the pertinent data can be ascertained. Comparisons of the values for the blood uric acid of the birds as determined in the different weeks disclosed variations such as are indicated in Tables I and II. However, many of the low values for uric acid, determined on the blood of birds in which the concentration of uric acid usually was found to be high, were obtained at times when the animals were sick. Some turkeys had enterohepatitis and others were not disposed to eat well at times when gouty tophi were actively developing.

The effect of feeding and of fasting on the blood uric acid of birds which did not have gout (Table III) indicates that the blood uric acid rises after a meal and that the amount of the rise is dependent on the nature of the diet. Much greater rises were obtained when diets contained an increased amount of protein or of urea. If the animal was then fasted, the blood uric acid decreased rapidly so that low values were obtained within twenty-four hours. During the next twenty-four hours there appeared to be a slight rise in the uric acid content of the blood. Similar changes were observed in animals with gouty tophi both in the active stage and in quiescent periods. The blood uric acid of gouty birds after a fast of twenty-four hours appeared to be slightly higher than that of normal birds but the values were small when compared to those usually found in examination of the blood of turkeys that had access to food. The blood uric acid of fasting gouty turkeys was found to be between 3.0 and 5.0 mg. per cent, while that of normal turkeys was between 1.5 and 4.0 mg. per cent.

If the turkeys were allowed free access to food, little difference was found in the uric acid content of the blood whether their exercise was or was not restricted by confinement in cages. The restricted animals did take less food, probably because the cages were in a building which reduced the hours of daylight so that these birds roosted longer than their outdoor neighbors. The concentration of uric acid in their blood, however, was not significantly different from that found in the outdoor birds which received the corresponding diet.

The uric acid content of the blood of the turkeys fed the diet of turkey mash only (Table I) varied but over a period of time was found to be remarkably consistent. Those to whose mash green leaves were added were found to have slightly less uric acid in the blood.

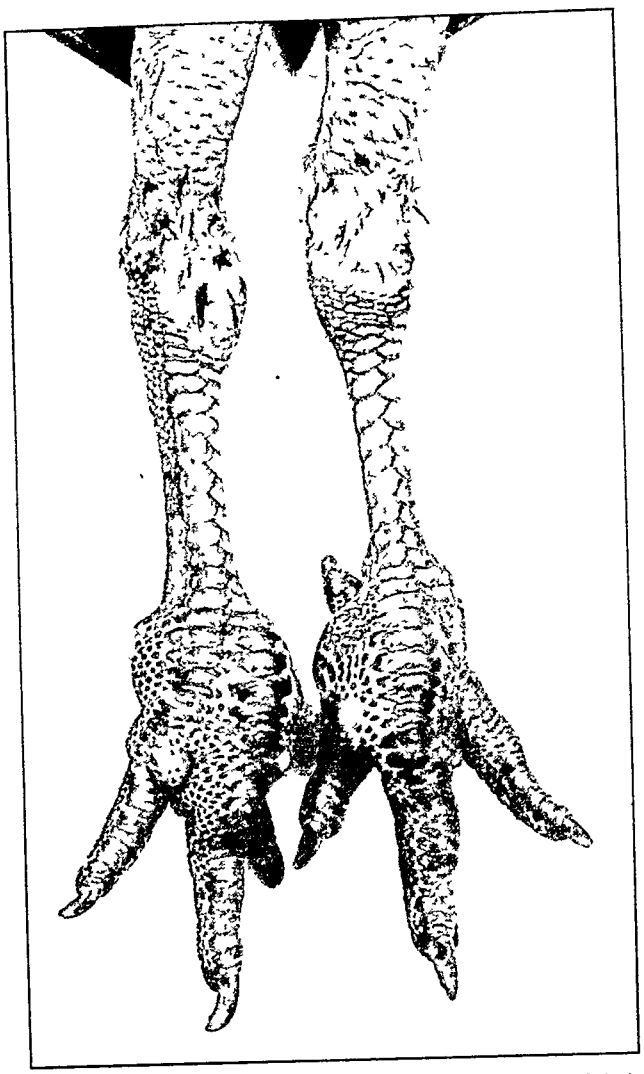


Fig. 1. Gouty feet of turkey which received a diet rich in protein, and injections of uranium (number 13, Table III).

but it is doubtful that any significance should be attached to this small difference. The blood of those birds whose food (cracker meal and turkey mash) contained less protein and more carbohydrate than was contained in the diet of mash and green leaves similarly contained a relatively small amount of uric acid. The addition of urea to the diet apparently increased the uric acid content of the blood above that which would be anticipated with the same diet less the added urea. Greater increases in uric acid were observed in the blood of birds fed the diet containing equal parts of turkey mash and horse flesh. A much wider range of variation in the value for uric acid in the blood was found among those birds which received diets which gave high values for uric acid in the blood.

The administration of cinchophen to birds which were receiving the diet of turkey mash and horse flesh was without effect on the uric acid of the blood. The values found were similar to those that had been obtained when the same bird had been given the same diet without cinchophen; the values also were similar to those obtained when other birds were given the same diet, without addition of cinchophen. The incidence of tophaceous gout and the course of the disease were likewise similar when birds were given this diet, whether or not cinchophen was added.

In the blood of birds that received uranium, values for uric acid were high. Similar results were obtained with the birds that received injections of lead. In the blood of most of the birds which received injections of uranium or lead the concentration of uric acid was higher than might have been anticipated when birds were given the particular protein rich diet employed in the experiment concerned. It should be noted that in the blood of about a third of the birds given uranium or lead the elevation of uric acid was about the same as in that of birds which were given the protein-rich diet only. Therefore, we feel that too much significance should not be placed on the effects of lead or uranium under the conditions of this experiment. Histologic examination of the kidneys of the birds that received lead or uranium disclosed very little abnormality. Only an occasional necrotic tubular cell, with some deposition of calcium could be found; these changes might be attributed to the action of either uranium or lead on the kidneys. Repeated examina-

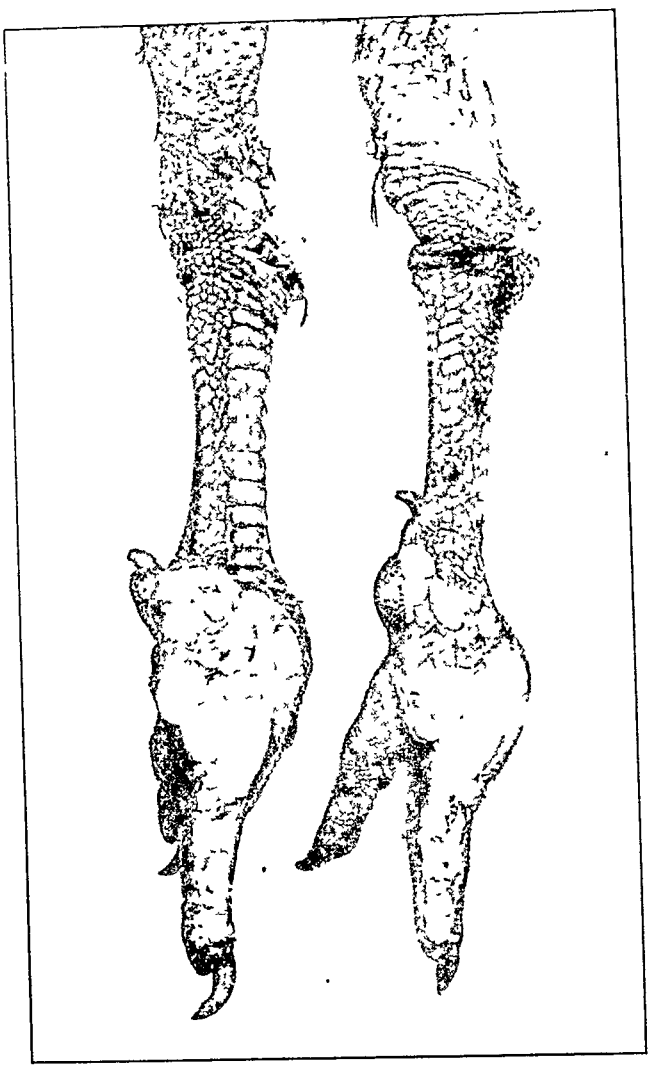


Fig. 2. Gouty feet of turkey, opened to show white areas of urate deposits.

TABLE II

Effect of treatment on blood uric acid of turkeys with protein-rich diet

Treatment	Bird	Blood uric acid, milligrams per cent			Duration, weeks	Tophaceous gout
		Average	High	Low		
None	19	12.4	29.7	5.1	46	+
	20	17.7	27.3	11.9	14	++
	21	19.3	27.8	10.6	14	++
	22	13.6	29.2	6.2	46	+
	23	22.9	33.2	16.1	9	+++
	24	21.0	29.9	12.3	12	+++
	25	14.6	19.1	8.9	8	0
	26	17.3	26.4	7.1	46	++
Cinchophen 1 gm. daily in food	27	22.8	26.6	15.3	17	+++
	28	15.6	28.5	7.2	46	+
	29	17.8	29.7	7.5	46	+
	30	17.5	28.0	7.1	40	++
Uranium 25 mg. intramuscularly three times a week	31	19.8	25.6	15.6	9	++
	32	19.0	28.6	8.1	26	+++
	33	22.6	37.2	13.0	9	+++
	34	21.4	28.6	15.3	15	+++
Lead 10 mg. intramuscularly three times a week	35	23.6	38.0	10.4	28	+++
	36	16.5	25.6	17.7	7	0
	37	23.5	36.0	13.0	12	+++
	38	21.1	35.4	14.4	12	+++

tions of the blood gave no evidence of changes attributable to these poisons.

Lesions of gout developed in nineteen turkeys of the group of twenty-six which received the diet especially rich in protein and in one of the four birds which received urea. No gout developed in any of the eleven birds which received the turkey mash alone or in those which received cracker meal or green leaves in addition to the mash. In all of the birds in which gout developed the value for the blood uric acid was 16 mg. per cent or more for the week or two preceding the appearance of lesions sufficiently characteristic to be considered definitely those of gout. A decrease in the amount of uric acid in the blood frequently occurred during the week or two after gout was apparent. At this time the birds usually took much less food than previously and later the blood uric acid increased when the animals regained their normal appetites. Subsequent loss of wellbeing occurred at times when new tophi appeared to be developing but the presence of old tophi seemed to produce no symptoms.

COMMENT

The first symptom of gout displayed by the affected birds was lameness and difficulty in arising after sitting prone. In the early stages the turkeys spent most of the day prone on the ground, in a manner that made it appear that pain was present or was at least associated with movement. The attacks of pain seemed intermittent, as the birds would move normally again after a few days and then several days later would resume their characteristic positions. Within a few days after the appearance of symptoms, small tophi usually could be observed on the feet. These tophi gradually enlarged, but the enlargement itself seemed to bear no relation to the symptoms observed. Some birds appeared to have pain when the tophi were enlarging but others had no symptoms accompanying the enlargement. We did not observe any material decrease

TABLE III

Effect of fasting on the uric acid content of the blood

Diet used	Bird	Uric acid in blood, milligrams per cent				
		Previous average with diet used	Three hours after feeding	Fasting 18 hours	Fasting 24 hours	Fasting 42 hours
Turkey mash	A	4.4	4.3	1.6	2.1	3.1
	B	5.4	5.9	2.7	2.7	3.7
Horse flesh and turkey mash	C	7.3	12.7	5.6	2.9	3.2
	D	12.2	12.5	8.2	4.1	4.1

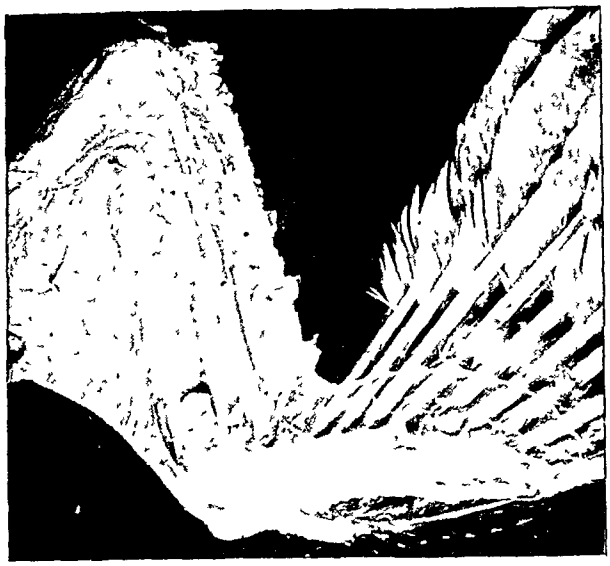


Fig. 3. Gouty tophi in wing of turkey which received a diet rich in protein, and injections of lead (number 17, Table III).

in the size of the large tophi, but small ones disappeared from time to time. Alteration of the diet, with subsequent reduction in the uric acid content of the blood, did not cause rapid diminution in the size of the tophi; although some of the tophi did disappear under these circumstances, others however, were unaltered.

The tophi and articular cavities contained masses of white, semisolid or paste-like material. Microscopic examination of this material disclosed masses of needle-like crystals, frequently arranged in sheaves. Examination of the tophi also revealed these crystals enclosed in connective tissue of varying density. The uric acid content of the pasty material, either from tophi or from the articular cavities, was found to be from 4 to 5 per cent of the moist weight of the material and from 20 to 30 per cent of its dry weight.

From the results obtained it is obvious that the uric acid content of the blood of turkeys under ordinary feeding conditions depends on the protein or the nitrogen content of the diet. The elevation of uric acid is probably not associated with the metabolism of nucleic acid since such elevation also occurred in the blood of birds which were fed urea. It appears probable that the major portion of the uric acid of the blood represents that which has been formed by the liver from urea, either that administered or that formed from the catabolism of protein. This is of course a special mechanism for the formation of uric acid in birds and reptiles and is not present in mammals.



Fig. 4. Gouty involvement of the tibiometatarsal joint of turkeys (numbers 18 and 19, Table III).

In some previous experiments (11) we observed that the yolks of eggs from our gouty birds were almost white, but that other birds of the same flock produced eggs with yellow yolks. In these experiments the addition of green spinach leaves to the diet produced eggs with yellow yolks but the level of uric acid in the blood was not reduced more than when carbohydrate was added to the diet. It seems probable that the gouty birds in our former experiments did not pick up green plants from their pen as did those not affected.

We have used eight female turkeys to one male in these experiments, so that our number of male turkeys is not sufficient to warrant conclusions as to the sex incidence of gout under these conditions. We could find no difference, on the basis of sex, in the amount of uric acid in the blood of birds which were receiving the same diet. Two of the birds in which gout developed were males and we saw no indication of resistance to gout in either sex. It appeared that gout developed after the value for the uric acid of the blood had remained at 16 mg. per cent or higher for several days. Severe cold weather might have precipitated some attacks of gout. Several birds had symptoms and tophi developed in them immediately following exposure to severe cold weather, after they had failed to have symptoms for several weeks when the value for the uric acid in their blood was in the neighborhood of 16 mg. per cent. In many other birds, however, gout developed without exposure to cold.

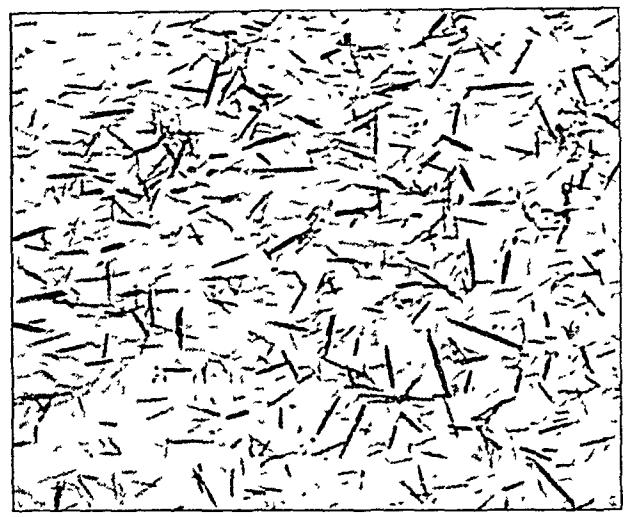


Fig. 5. Crystals of urates expressed from gouty tophus of turkey (x750).

SUMMARY

The blood uric acid of turkeys is elevated after feeding and is diminished to a low level after fasting. When free access to food is allowed the value for the uric acid in the blood is usually found to be several times that for the fasting bird. The level of the blood uric acid is greatly increased by additions of protein or of urea to the diet.

Symptoms of gout and the development of gouty

tophi on the extremities and gouty depositions in the articular cavities occur in turkeys if the uric acid in the blood is maintained at a high level for several days.

Administration of cinhcophen appeared to have no effect on the uric acid content of the blood or on the cccurrence or symptoms of gout in those animals in which gout was present.

Administration of nephrotoxic agents (uranium and lead) appeared to increase the uric acid content of the blood slightly and to hasten the appearance of gout.

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Spontaneous Hyperinsulinism Due to Pancreatic Adenoma in a Patient with Carcinoma of the Sigmoid -- a Catastrophic Conjunction*

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SPONTANEOUS hyperinsulinism might be called the "isomer" of diabetes. In diabetes a lack of endogenous insulin results in hyperglycemia. The mirror condition entails an excessive secretion of endogenous insulin with varying degrees of hypoglycemic shock. Clinical types of hyperinsulinism have been well defined by Seale Harris (1), who points out that more cases are not recognized because physicians fail to watch for them. However, the general symptoms are familiar enough in the ordinary case and need not be further reported in the literature.

The instance here reported showed two independent lesions in a single patient: one benign, causing devastating symptoms; the other malignant with very few symptoms; both conspired to produce death.

The significance of the history in leading to the diagnosis can only be appreciated if one remembers that orthodox Jewish custom requires a fast for twenty-four hours on the Day of Atonement.

History: On October 27, 1935, a white male, age 45, was sent by Dr. H. Fine to the service of Dr. Edwin Heller with the chief complaint of "spells" and hemorrhoids. On first examination the following facts were determined concerning him:

Being a pious man, it had been his custom to spend the Day of Atonement (Yom Kippur) in synagogue fasting. On this holiday preceding his admission, his wife came to synagogue about eleven o'clock in the morning and found him in a kind of walking stupor. He did not recognize her; he did not respond intelligently to questions; he seemed to be "out on his feet." He was taken to a physician's office but on the way was made to drink a cup of coffee so that within half an hour after arriving at the doctor's office he was perfectly rational. At five o'clock on the morning of his admission his wife was awakened by his heavy breathing and found him unconscious. He did not regain consciousness for two and one-half to three hours.

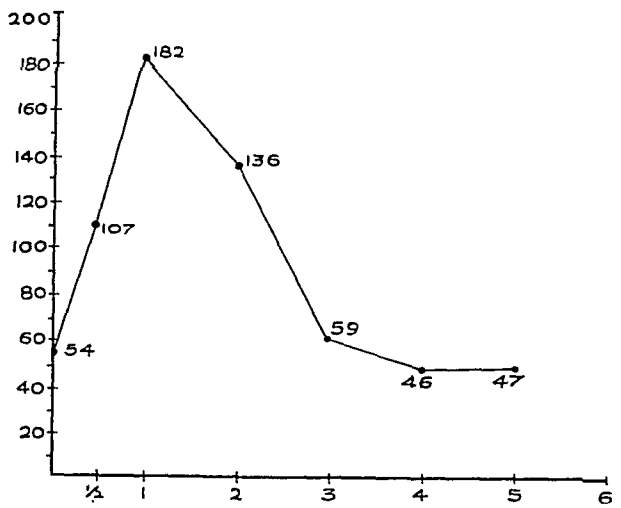
This story aroused the suspicion of what later proved to be the true diagnosis, and the patient was deliberately asked concerning his eating habits and his sensations when



Fig. 1. Low power microphotograph showing enlarged islands of Langerhans within the adenoma.

*From the Medical Wards and Laboratories of the Jewish Hospital. Submitted May 29, 1936.

required to go without food beyond the usual mealtime. His answer was that for many years hunger had always forced him to eat immediately because failure to do so would cause severe pain in his stomach and a sense of weakness. The patient was a mentally alert, obese, white male of apparently 45 to 50. There was no abnormal physical finding except the hemorrhoids. The *diagnosis of spontaneous hyperinsulinism* was made at this examination clinically. Two nights later he became suddenly unconscious. A specimen of blood was obtained before treatment was instituted. Its sugar content was 30 mgm. per 100 c.c. The Resident reported that 10 c.c. of 50% glucose intravenously brought the man back to complete consciousness even before the injection was finished. The blood sugar curve on a six hour observation is as follows and seems identical with those reported in many cases by Dr. Seale Harris:



Graph 1. Five hour glucose tolerance test. Ordinate shows blood sugar in milligrams per hundred c.c. Abscissa shows time interval in hours. The test had to be terminated at the fifth hour due to symptoms of oncoming shock.

Diagnostic discussion: Having established the fact of hyperinsulinism, our next quest was its cause (2, 3).

1. Was it the pituitary? No, for the X-ray Department reported a normal *sella turcica.*

2. Was it deficient liver glycogen? No, for with a fasting blood sugar of 68 mgs., one c.c. of adrenalin by hypodermic raised the blood sugar to 100 mgs. within half an hour without feeding any sugar.

3. Was it interference with the regulating center, *i.e.,* over-activity of the parasympathetics? No, for the pulse remained normal, the pupils normal, and the eye grounds showed no evidence of intracranial pressure.

Thus, we were forced to conclude, by eliminating other factors to the best of our ability, that intrinsic over-activity of the insular pancreatic tissue (adenoma) was basic in this patient's symptoms (4).

The patient's hemorrhoids had been bothering him for several years but only recently began to bleed, and seemed to us at first not a very significant part of the history. With X-ray and proctoscopic help we investigated further and found that the underlying condition was a polypoid cancer low in the sigmoid, for which we advised surgery. After a few days spent arranging his personal affairs, the patient returned to Dr. Frank Block's surgical service for operation. He had a stormy but complete convalescence from his first stage surgical episode. Dr. Block was asked to palpate the pancreas in an effort to discover an adenoma but reported that none could be felt. Later developments certainly corroborated this report for it was only by dint of thorough search that the lesion was finally discovered at the autopsy. Forty-eight hours after the second stage surgical procedure the patient suddenly collapsed and died.



Fig. 2. High power microphotograph from edge of islands shown in Fig. 1, demonstrating the exclusively insulinogenic type of cell present.

The *diagnosis of sigmoid adeno-carcinoma* gave credence to the possibility of pancreatic metastasis. We felt that, theoretically at least, such a metastasis should *decrease* rather than *increase* insulinogenic activity. Consequently, our *clinical diagnosis* at death was: "Adeno-carcinoma of the sigmoid with probable pancreatic adenoma."

AUTOPSY (D.B.F.)

At autopsy the pancreas was smaller than normal, being about half the size one would expect in a patient of this man's weight. With the fat removed it was remarkably thin and flat and in its tail there was a firm gray nodule the size of a pea. The histo-pathologic study of this nodule proved it to be an adenoma involving the islands of Langerhans. No carcinoma cells were present. The histo-pathology of the head of the pancreas indicated a marked interstitial fibrosis but no adenomatous tissue was discovered in this location.

It was found that all malignant tissue in the bowel had been removed. The pelvic peritoneum was walled off with easily broken adhesions. The parietal peritoneum was reddened with roughly 100 c.c. of blood-tinged fluid incarcerated here.

The rest of the autopsy was negative.

SUMMARY

We report a case of spontaneous hyperinsulinism due to pancreatic adenoma, coexistent with a carcinoma of the recto-sigmoid. The presence of these separate entities was recognized before operation and they were proved at autopsy.

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Enzymic Efficiency in Avitaminosis

III. Influence of Vitamin B_1 and G Deficiencies on the Concentration of Blood and Tissue Enzymes*†

By

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IN previous publications we reported that in vitamin B_1 deficiency there is a reduction in the concentration of pancreatic lipase and esterase (1) but that this avitaminosis produces no demonstrable changes in the proteolytic enzymes trypsin and erepsin (2).

We have since extended our observations to other enzymes and other deficiency diseases. The additional enzymes studied are: pancreatic amylase; hepatic lipase and esterase; blood serum esterase, amylase and phosphatase; also kidney phosphatase in vitamin B_1 deficiency and in a few groups in a deficiency of the vitamin B complex.

In this communication results are submitted on vitamin B_1 and G deficiencies; also on a deficiency of the vitamin B complex. This work is grouped in order to determine whether there is any correlation between enzyme changes and the deficiency of several factors of the B group and uncomplicated vitamin B deficiency.

Throughout this study the experiments were carried out in pairs, using litter mates of the same sex and restricting the control to the same plane of nutrition as the avitaminotic animals.

METHODS OF PROCEDURE

The technique for the titration of the various enzymes was the same as recently employed in investigations of Enzymic Changes in Malignancy (3).

The criterion for B_1 deficiency was extent of loss of weight. In addition to 18 to 20 groups used in this study, polyneuritis was produced in the majority of 30 groups of animals on the ration of Ammerman and Waterman (4). As a vitamin B_1 supplement for the control animals graduated doses of a concentrate furnished by the Eli Lilly Research Laboratories were used. The controls for the polyneuritic rats received daily 10 γ of Merck's crystalline vitamin B_1.

In the G experiment's a daily allowance of 20 to 40 γ of crystalline B_1, supplementing a diet deficient in the vitamin B complex, proved a successful procedure for the production of dermatitis. The term G includes what the English workers at present recognize as flavin plus B_6 (5).

There were approximately 4,000 titrations carried out in this investigation. It is, therefore, impossible to submit detailed data. Furthermore, since the changes in enzyme concentration are not, with a few exceptions, proportional to loss of weight expressed in per cent of body weight or to the severity of the polyneuritis or dermatitis, all the results have been averaged and summarized which are presented in Tables I to III.

In the compilation of the tabular data it was considered important to show not only the per cent of increase or decrease in enzyme concentration of the pathologic animals compared with their litter mate controls, but also to indicate the per cent of the groups of animals which showed the particular change.

VITAMIN B_1 DEFICIENCY

Influence of the Extent of Loss of Body Weight and Polyneuritis on the Concentration of Blood and Tissue Enzymes: The animals were 40 to 55 days of age and weighed 110 to 150 gm. The losses of weight ranged from 4 to 47 expressed as per cent of the body weight. The results are quite fluctuating among individual animals; but, on the whole, there is no correlation between extent of loss of body weight and enzyme concentration either in the blood or in the tissues. Neither does the degree of polyneuritis exert any effect on concentration of blood serum and tissue enzymes. From an analysis of Table I it is apparent that there is a marked decrease of pancreatic esterase and an appreciable decrease in the concentration of pancreatic and hepatic lipase. Why the albino rat should be less efficient in the digestive efficiency of esters than true fats, the esters being simpler substances than fats, is difficult to explain.

Polyneuritis associated with only small losses of body weight shows no noteworthy changes in enzyme concentration. The small changes in the concentration of blood serum esterase in vitamin B_1 deficiency is in accordance with the results reported by Green (6).

VITAMIN G DEFICIENCY

The majority of the groups of animals for this study were one and one-half to two months old and weighed 95 to 110 gm. There were also a number of groups selected from older stock, four to five months old, and weighing 150 to 210 gm. The losses of weight ranged from 2 to 35 per cent of the body weight. Sixty per cent of the pathologic animals developed dermatitis. Neither extent of loss of weight nor severity of dermatitis had any noteworthy influence on concentration of blood or tissue enzymes.

An examination of Table II shows a 20.9 per cent decrease in the concentration of blood serum phosphatase. We have no explanation for these results in view of the fact that in a deficiency of the vitamin B complex there is an average 26.3 per cent increase in the concentration of this blood serum enzyme (Table

*From the Laboratory of Agricultural Chemistry, University of Arkansas, Fayetteville.

†Research paper No. 344, Journal Series, University of Arkansas.

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TABLE I

Influence of vitamin B_1 deficiency on the concentration of blood and tissue enzymes of the albino rat

ENZYME	Number of groups studied	Average for all groups P	Average for all groups C	Per cent decrease in Pathological	Per cent increase in Pathological	Per cent animal groups showing decrease	Per cent animal groups showing increase	Per cent animal groups showing no change
Blood serum amylase*	20	19.1	21.8	12.4	—	55.0	30.0	15.0
Blood serum esterase‡	20	11.0	12.1	9.1	—	70.0	20.0	10.0
Blood serum phosphatase*	18	47.7	42.4	—	12.5	38.9	61.1	0.0
Kidney phosphatase*	20	14.9	17.4	14.4	—	15.0	85.0	0.0
Pancreatic amylase*	20	302.0	303.0	0.0	0.0	50.0	30.0	20.0
Pancreatic lipase§	20	107.0	139.0	23.0	—	90.0	10.0	0.0
Hepatic lipase§	20	19.5	24.5	20.5	—	65.0	20.0	15.0
Pancreatic esterase‡	20	7.6	13.5	43.7	—	80.0	15.0	5.0
Hepatic esterase‡	19	29.9	31.8	6.4	—	42.1	57.9	0.0

*Expressed as units. ‡Expressed as mg. butyric acid. §Expressed as mg. oleic acid.

III) and a small increase in this constituent in vitamin B_1 deficiency.

DEFICIENCY OF VITAMIN B COMPLEX

This investigation was carried out with two groups of animals of different ages. One group was four to six weeks old and weighed 65 to 85 gm. and the other two to five months old and weighed 130 to 200 gm. The losses of weight ranged from 7 to 34 per cent of the body weight.

The appreciable increase in the concentration of the blood serum phosphatase may be correlated with pathologic changes in osteogenetic tissues found in this avitaminosis (7), since blood serum phosphatase is high in bony disorders (8). We would like to state, however, in this connection, that work in progress indicates that, unlike the experience of investigators in human rickets (9), we are finding very little increase in concentration of blood serum phosphatase in experimental rickets, which is in harmony with the recent observations of Scoz (10).

There is also an appreciable decrease in hepatic lipase in a deficiency of the vitamin B complex. Although we previously found no change in ereptic activity in vitamin B_1 deficiency, 60 per cent of the groups in vitamin B complex deficiency show a 27.7 per cent increase, the significance of which is also not clear.

TABLE II

Influence of vitamin G deficiency on the concentration of blood and tissue enzymes of the albino rat

ENZYME	Number of groups studied	Average for all groups P	Average for all groups C	Per cent decrease in Pathological	Per cent increase in Pathological	Per cent animal groups showing decrease	Per cent animal groups showing increase	Per cent animal groups showing no change
Blood serum amylase*	36	26.5	24.3	—	9.1	52.8	47.2	0.0
Blood serum esterase‡	31	18.9	19.8	4.5	—	38.7	41.9	19.4
Blood serum phosphatase*	28	45.0	56.7	20.9	—	78.6	21.4	0.0
Trypsin*	35	50.0	53.0	—	6.0	51.4	37.1	11.5
Erepsin*	36	27.5	27.5	0	0	41.7	55.5	2.8
Pancreatic amylase*	36	274.0	282.0	2.9	—	52.7	38.9	8.4
Pancreatic lipase§	36	162.9	165.1	1.3	—	66.6	25.0	8.4
Hepatic lipase§	35	28.4	28.6	0.8	—	48.5	48.5	3.0
Pancreatic esterase‡	36	15.1	17.1	13.2	—	69.4	27.7	2.9
Hepatic esterase‡	36	37.6	37.2	—	1.1	30.6	61.0	8.3

*Expressed as units. ‡Expressed as mg. butyric acid. §Expressed as mg. oleic acid.

TABLE III

Influence of vitamin B complex deficiency on the concentration of blood and tissue enzymes of the albino rat

ENZYME	Number of groups studied	Average for all groups P	Average for all groups C	Per cent decrease in Pathological	Per cent increase in Pathological	Per cent animal groups showing decrease	Per cent animal groups showing increase	Per cent animal groups showing no change
Blood serum amylase*	27	25.6	23.3	—	10.0	45.0	52.0	3.0
Blood serum esterase‡	26	14.3	15.2	5.9	—	62.0	38.0	0.0
Blood serum phosphatase*	27	57.5	45.5	—	26.3	26.0	74.0	0.0
Kidney phosphatase*	9	15.3	16.1	5.0	—	56.0	44.0	0.0
Trypsin*	20	63.6	54.8	—	13.7	20.0	75.0	5.0
Erepsin*	20	31.7	22.9	—	27.7	25.0	60.0	15.0
Pancreatic amylase*	29	263.0	260.0	—	1.1	51.7	30.2	14.1
Pancreatic lipase§	28	154.0	171.0	9.9	—	67.8	21.4	10.8
Hepatic lipase§	28	20.8	20.5	—	1.5	39.3	50.0	10.7
Pancreatic esterase‡	29	15.6	17.4	—	11.4	55.1	41.4	3.5
Hepatic esterase‡	29	37.7	31.5	—	19.7	20.7	79.3	0.0

*Expressed as units. ‡Expressed as mg. butyric acid. §Expressed as mg. oleic acid.

SUMMARY

1. Summarizing the results of this investigation, there is no noteworthy change in the digestive efficiency of either the proteolytic or the amylolytic enzymes in vitamins B or G deficiency, or in a deficiency of the vitamin B complex.

2. There is a marked decrease in the digestive efficiency of pancreatic esterase and a moderate decrease in the concentration of pancreatic and hepatic lipase in vitamin B_1 deficiency, suggesting a disturbance in digestion of fats in this avitaminosis.

3. An appreciable increase was observed in concentration of blood serum phosphatase in a deficiency of the vitamin B complex.

4. With the exception of a 20 per cent decrease in the concentration of blood serum phosphatase, no noteworthy changes in concentration of blood or tissue enzymes were found in vitamin G deficiency.

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Enzymic Efficiency in Avitaminosis

IV. Influence of Vitamin A Deficiency on Concentration of Blood and Tissue Enzymes.*†

By

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VITAMIN A deficiency was produced on a dietary regime previously outlined (1). The same biological procedure of paired feeding, using litter mates of the same sex and controlling the plane of nutrition as employed previously (2) was adopted in this investigation. The animals were two to four months old when started on the experiments and weighed from 112 to 176 gm. Large animals were selected, in order to have the opportunity to observe various stages of this avitaminosis by lengthening the depletion and experimental periods. Various stages of vitamin A deficiency were encountered, i.e., prolonged maintenance to large losses of weight; the persistence of the cornified vaginal epithelium in the females; incipient ophthalmin to severe eye lesions; and various combinations of such symptoms. The losses of body weight ranged from 1 to 42 per cent.

There was a total of 1832 titrations carried out in this study, all of which results were averaged and summarized in Table I, since extent of losses of weight and severity of eye lesions had no specific influence on enzyme concentration either in blood or tissues.

Table I reveals two outstanding facts: the marked reduction in blood serum esterase and the large increase in hepatic lipase. Our results on the blood serum esterase are in agreement with the work of Green (3). While the increase in hepatic lipase occurred only in 47.9 per cent of the pathologic animals, almost an equal proportion of decreases having taken place, the increases that did occur were of a high magnitude—in some cases they were as much as 500 per cent greater than in the litter mate controls on the same plane of nutrition. The large increases in the concentration of liver lipase were found mainly in animals that showed either prolonged maintenance of body weight or early symptoms of vitamin A deficiency. Some of these pathologic animals showed no other symptom than a cornified stage of the vaginal epithelium. Great care was taken in the preparation of the liver tissue for extraction of enzyme with 25 per cent glycerol. It was first washed in distilled water, the blood squeezed out by making a small incision in the organ and then dried on filter paper. The differences in titrations which were of a range of several hundred per cent among pathologic animals of different groups could not be due to varying amounts of blood present in the livers, particularly, since we found only traces of lipase in the blood.

If the animal organism has the capacity to transform esterases into lipases, one might argue that the disappearance of blood serum esterase and the simultaneous accumulation of hepatic lipase is due to the former enzyme being changed to the latter. Since, however, the increases of hepatic lipase in the cases that showed several hundred per cent increase are entirely out of proportion to the decreases in blood serum esterase, it is hardly probable that this mechanism is in operation.

In the presentation of the results of our enzyme studies in avitaminosis completed to date, it is of the greatest interest to present the facts, the significance of some of which may become clear in later years. It is at least encouraging that certain enzyme studies in disease are being successfully applied clinically. For instance, recent enzyme studies (4) indicate a reduced concentration of blood serum enzymes in victims of food allergy, which according to the investigators account for their being unable to split the foreign proteins into amino acids. The foreign proteins then enter the various tissues and produce irritation, hence the allergic reaction. Such victims seem to respond favorably to commercial pancreatic preparations which stimulate the production of the blood enzymes.

The significance of the marked decrease of blood serum esterase in vitamin A deficiency, while not apparent at present, may become clear later when a study of vitamin A pathology is approached from another angle.

An appreciable reduction in hepatic esterase is also apparent from Table I. Whether hepatic esterase is transformed into hepatic lipase is also only a suggestion which requires proof.

Although it has been generally believed that in vitamin deficiency diseases there is a great loss of digestive efficiency, the results of our work to date disclose only a mild disturbance in the digestion of fats in one avitaminosis, namely, vitamin B_1 deficiency. Since the American diet is composed largely of highly milled cereals and is not sufficiently supplemented with fresh fruits, vegetables, and dairy products, it is possible that a large proportion of the population of this country is not only on the border line of vitamin requirements, but is also not receiving the optimum intake of certain mineral elements. Sherman, for instance, emphasizes the deficiency of calcium in the American diet (5), which is an indication of the in-

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†Research paper No. 385, Journal Series, University of Arkansas. Submitted April 24, 1936.

TABLE I

Influence of vitamin A deficiency on the concentration of blood and tissue enzymes of the albino rat

ENZYME	Number of groups studied	Average for all groups P	Average for all groups C	Per cent decrease in Pathological	Per cent increase in Pathological	Per cent animal groups showing decrease	Per cent animal groups showing increase	Per cent animal groups showing no change
Blood serum amylase*	47	27.2	30.9	12.0	—	66.0	31.9	2.1
Blood serum esterase‡	41	8.2	13.7	40.1	—	85.4	9.7	4.9
Blood serum phosphatase*	44	29.6	31.5	6.3	—	56.8	38.6	4.6
Trypsin*	42	45.0	45.0	0	0	45.2	50.0	4.8
Erepsin*	38	23.0	25.0	8.0	—	68.4	26.3	5.3
Pancreatic amylase*	53	283.0	287.0	1.6	—	41.5	37.7	20.8
Pancreatic lipase§	48	153.0	162.0	5.5	—	58.4	35.4	6.2
Hepatic lipase§	48	47.8	36.8	—	33.5	43.7	47.9	8.3
Pancreatic esterase‡	48	18.0	18.7	3.7	—	44.7	48.9	6.4
Hepatic esterase‡	47	22.1	27.2	19.5	—	23.4	76.6	—

*Expressed as units. ‡Expressed as mg. butyric acid. §Expressed as mg. oleic acid.

sufficient consumption of milk which provides the factor of safety in so far as calcium is concerned. What influence avitaminosis would exert on enzymic efficiency when handicapped by deficiency of mineral elements, as it apparently exists in the American diet, deserves investigation. It is possible, however, that there is a deficiency of peptic activity in avitaminosis. Our next efforts then will be directed in this field.

SUMMARY

In vitamin A deficiency there is a marked decrease in the concentration of blood serum esterase, an appreciable decrease in hepatic esterase, and a marked increase in hepatic lipase.

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SECTION IV—*Roentgenology*

Roentgenographic Studies of the Mucous Membrane of the Colon
II. Colitis

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NOT long ago Alvarez wrote (1): "In nine out of ten cases of colitis we cannot find the remotest sign of inflammation in the bowel, the colon looks perfectly normal. The patient is constipated and there was never any diarrhea."

This is an interesting commentary on our knowledge of colitis. We have to depend for the most part on clinical observations for its diagnosis. Pain, gas, change in frequency of bowel movements (constipation or diarrhea) and change in the consistency of the stools with pathological findings (presence of mucus, blood and bacteria) are the commonest findings.

It is well known that depending upon the activity of the process only some of these symptoms need be present. Different authors have endeavored to show

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Fig. 1. A. Simple chronic colitis. Tape-like formation of the mucosa. (Case 1).

changes of the intestines by roentgenographic examination. The routine method shows only those changes which are connected with deformities in the contours of the bowel. Therefore, any method which gives us more information should be welcomed. We have used the "surface technique" in studying colitis, a technique which we described in a previous paper (2).

Surface studies (mucosal) in colitis formerly were performed only rarely. As we outlined in a former presentation (2) the inner surface of the colon is not flat but has folds, and its pliability permits many different changes in appearance. Knothe (3) believes that the different changes found in simple colitis and ulcerative colitis represents various stages of the same disease. We do not feel warranted in taking such a definite stand because the clinical syndrome and the roentgenographic findings are in our opinion too strikingly diverse to represent the same disease.

Chaoul (4) claims that there are no definite roentgenographic findings in simple colitis, that hypertonicity of the colon appears to be the main reason why it is difficult to obtain good roentgenograms. In ulcerative colitis, he finds massive infiltration of the wall of the gut, "stripes" and "marble like" patterns of the mucosa visible through the gas content of the bowel.

Lups (5) in his excellent paper uses different methods: he shows cases examined by the double contrast enema method and also specimens of surface technique roentgenograms in cases in which later autopsies were obtained. He points out, that slight serration, seen after the complete filling method, was not caused by any pathologic process, which could be shown at autopsy. His findings might have been caused by fecal matter which very often adheres firmly to the colon wall in spite of several cleansing enemas, as Fineman and Snyder have shown in their exhibit of 1934 at the Graduate Fortnight of the New York Academy of Medicine. These difficulties must be taken into consideration in any attempt to appraise changes of the mucosal surface of the colon. The important factor therefore in a study of the colon is the appearance of the single mucosal fold as well as of the entire mucosal pattern of the bowel wall.

To date, in the diagnosis of colitis undue stress has been laid upon spasm. We consider spasm to be only a secondary sign. Spasm may be due to the following causes: (1) those entirely extrinsic to the colon, such as ulcer of the stomach or the duodenum, cholecystitis, inflammatory lesions or calculi of the gall bladder or in genito-urinary tract; (2) every organic change in the colon wall produces spasm as in the lesions of colitis, tuberculosis or tumor; (3) every irritation from the content of the gut may have a similar effect; (4) the contrast enema itself, hard fecal matter, gas and parasites need only to be mentioned. As a like effect may be due to so many different causes, one must conclude that spasm can be utilized diagnostically, only as a secondary sign, the importance of which is that its manifestations often are the chief and only cause of discomfort to the patient. A "spastic colon" may be painful and treatment may relieve much of the discomfort. But so far as roentgen diagnosis is concerned spasm has lost its former significance. It would seem, therefore, that a study of the mucosal aspect of the colon now is more valuable, provided certain carefully considered, standard points of the



Fig. 1. B. Simple chronic colitis Appearance of the same case after routine barium enema. (Case 1).



Fig. 2. Nodular hyperplastic colitis. Case 2.

interpretation are recognized and become established.

"Colitis" is such a complex subject that we shall not attempt to cover the field in this communication. Here we shall attempt to present merely our observations on the mucosal changes which we have found in certain instances. We are well aware that many unusual findings of the colon mucosa demand explanation.

CASE REPORTS

(1) Simple chronic colitis. Case 1. The patient, a female, 61 years old, for several years experienced "nervous" diarrhea. In the past few months, she developed constipation alternating with diarrhea. She complained of pain in the left upper abdominal quadrant, gas and rumbling sensations in the left flank. Mucus was observed in the stools, but blood never was observed. Her condition could only be controlled by a restricted diet. The diagnosis was simple chronic colitis.

Fig 1B shows the colon completely filled with barium. No definite pathology is observed. Fig. 1A shows the mucous membrane of the same segment of the colon. One observes that this section of the gut exhibits no haustration. The colon still retains transverse folds, but these folds are shortened and are reduced to the average width of the intestine. The *pattern of the surface* has changed to the form of an uneven mosaic. The single fold has very well defined borders but the pattern is different from the normal The contraction of the colon after evacuation is different from that of the normal. The lumen remains free. The complete filling demonstrates that the gut is not a rigid tube, for its distention after barium enema is normal. Only its power of contraction has become impaired so that it resembles an old rubber hose, which has lost its elasticity. These findings indicate the loss of elasticity of the colon particularly with respect to its contractible functions.

Case 2 (courtesy of the Gouverneur Hospital) demonstrates the mucosal pattern *(Fig. 2)* of a patient affected with colitis for the past ten years. He experiences diarrhea alternating with constipation but never had he noticed mucus or blood in the stools. The patient was on a restricted diet, but continued to have pains in the left lower abdominal quadrant.



Fig. 3 (Case 3). Ulcerative colitis, early stage.



Fig. 4. (Case 4). Ulcerative colitis. Complete filling. No detail visible.

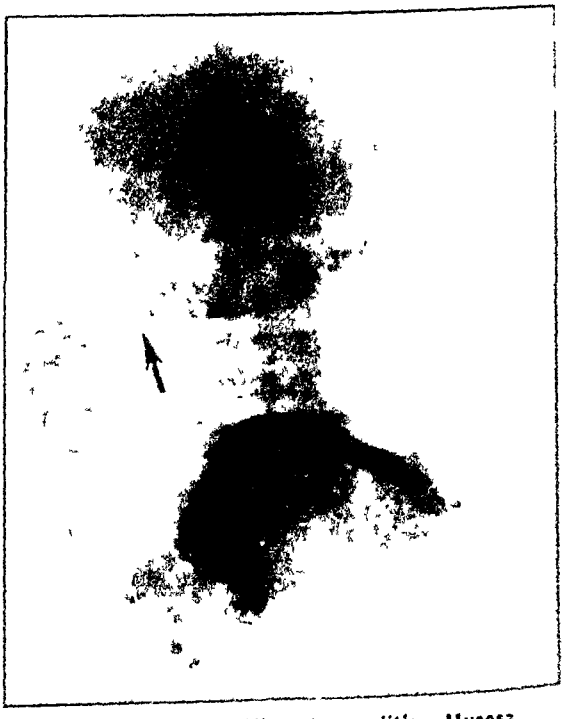


Fig. 5. (Case 4). Ulcerative colitis. Mucosa.



Fig. 6. Ulcerative colitis. (Case 5). Completely filled colon.

Physical examination revealed a palpable and tender sigmoid At the time of the roentgen examination of the colon the patient felt fairly well but recently had been rather constipated The mucosal roentgenogram shows a nodular appearance of the sigmoid, shortening of the rugae and absence of transverse rugae. The appearance of the mucosa may be likened to a well worn and uneven

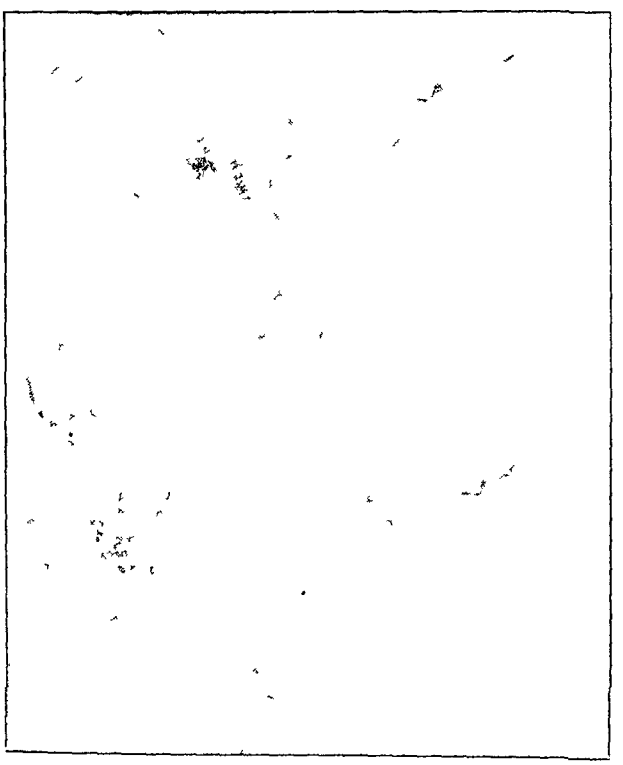


Fig. 7. Ulcerative colitis (Case 5). Mucosa.



Fig 8. Detail of the transversum of Fig. 7. (Case 5).

cobble-stone pavement. The irregular elevations are not quite so distinct as in a true case of polyposis. This nodular hyperplastic type of mucosa probably is a late stage of a chronic, simple colitis.

(2) Ulcerative colitis. Case 3 The patient clinically had an ulcerative colitis of short duration The diagnosis was established by proctoscopy. Blood was present in the stools.

The X-ray examination, after opaque enema, revealed no gross pathology. The post-evacuation roentgenogram *(Fig. 3)* revealed granular changes of the rugae, which otherwise were normal. In an adjacent haustrum one can observe an irregular mucosal surface showing absence of normal mucosal folds, but it will be noted that the haustrum is not impaired; longitudinal rugae connecting the haustrae are present The patient progressed through a short, uneventful recovery from this attack.

Case 4. (Through the courtesy of Dr. H. G. Jacobi) shows the colon of the patient, who was ill for about two weeks. He had blood and mucus in the stools. He suffered from diarrhea and pain in the abdomen. There was tenderness in the right side of the abdomen.

The colon after an opaque enema did not reveal any pathology *(Fig 4)*. The mucosal roentgenogram *(Fig. 5)* indicated that the right segment of the transverse colon

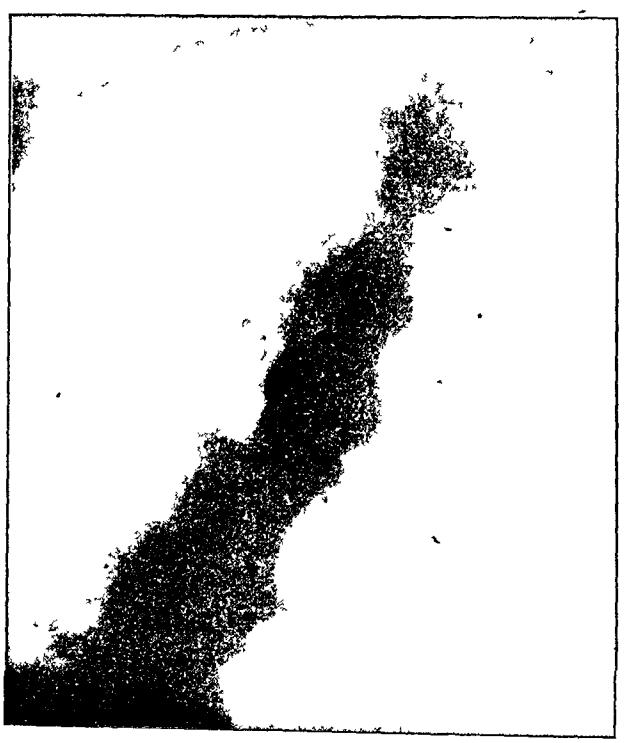


Fig. 9. Detail of the descendens of Fig 7. (Case 5). Ulcerative colitis.

had a dotted, marble-like surface pattern, such as has been described by Chaoul. Otherwise the transverse colon had a normal "barbed-wire" appearance.

This is an instance of localized colon ulceration at a relatively early stage. The patient recovered from this attack in about ten days after his Roentgen study.

Case 5. (Through the courtesy of Dr. A. Bassler). A patient, approximately aged 60, was ill for several years. He had blood and mucus in his stools and had experienced very frequent attacks of diarrhea for the past four months. The question of neoplasm arose because of the patients general condition.

Fig. 6 shows the completely filled colon. This is normal except for several diverticula located in the sigmoid segment. The mucosal studies *(Fig. 7)* however reveal widespread surface pathology. Every part of the colon suggests abnormal patterns, with the exception of the cecum of the ascending colon; these are normal. The transverse colon exhibits a blurred pattern, due to broad, cushion-like swollen rugae *(Fig. 8)*. Transverse rugae are still present. The descending colon *(Fig. 9)* reveals an irregular, undermined surface with small fistulae extending into the deeper layers of its wall. The changes in this segment are similar to those which Knothe (3) described. The anomalies are not due to spasm but to actual pathology of the mucosa and the adjacent mural layers. The sigmoid exhibits diverticula with broad swollen mucosa between them. This is an instance of an advanced, chronic colon ulceration in association with diverticulosis.

DISCUSSION

In this roentgen study of the mucosal anomalies present in colitis this special technique was employed in such cases, which did not exhibit pathology when the barium enema or the progress films alone were employed, but when clinically colon disease seemed to exist. After the colon had been coated with a thin layer of opaque substance, we were able to demonstrate various abnormal mucosal patterns, which suggested localized or general surface lesions or which indicated that, in spite of clinical symptoms, such did not exist.

In simple chronic colitis the mucosa shows changes of nearly all of its folds. The transverse rugae are shortened, they are no longer so distinct as normally. The longitudinal rugae between the transverse rugae disappear. The mucosa has a ribbon like character. The crevasses are not deep, so that in the early cases the colon shows only very faint traces of contrast substance between the folds. In colitis of very long standing but accompanied only by mild symptoms, we were able to demonstrate a nodular, hyperplastic type of mucosa. Probably this is the final stage of the affection.

In ulcerative colitis we observed various types of mucosal change. We were able to demonstrate in one of our patients the different stages of the disease in different segments of the same colon. Early in ulcerative colitis, the general mucosal pattern grossly is unchanged and shows only granular changes on the surface of some of the rugae; later on, a marble-like pattern develops. In severe and chronic ulcerative colitis, the rugae become broad and swollen, or the surface becomes entirely irregular. Small fistulae penetrating into the deeper layers of the gut may be present; these represent undermining of the mucosa. It is interesting to note that unless the ailment is far advanced, the transverse rugae always are present. This is an entirely different observation from the picture exhibited in the mucosal pattern in simple colitis.

In instances of simple colitis, we noted a marked loss of tonicity of the bowel. The lumen was wide open but the haustration had disappeared. The colon lost part of its elasticity. Distension was still possible as proved when it was filled by the barium enema. However, the capacity for normal contraction definitely was impaired. In simple colitis the colon was never observed as rigid or hose-like. However, in ulcerative colitis, impairment of the elasticity was not shown to be present in the early stages; however it is less evident in the late stages of the disease; indeed in advanced instances, the entire colon wall becomes hardened by inflammatory disease; in the healing from such areas of extensive fibrosis may wholly supplant normal mucosal structures and leave a firm rigid, nonfunctioning gut, with or without local areas of stenosis. No mucosa is present in such circumstances, since no trans-mucosal pattern can be shown.

We believe that such observations as we have carried out may improve our understanding of certain clinical symptoms in all forms of colitis. We trust that more extensively this new roentgen technique (so tremendously elaborated by French, Danish and Scandanavian workers) will become more general in this country, so that by comparative roentgen studies, backed by clinical observations and above all, by laparatomy or autopsy records, more reliable interpretative data than now is possible, will be available. It is highly desirable that clinicians better may be able to correlate clinical symptoms and signs, and the results of physical and laboratory examinations with roentgen studies—particularly such studies as are planned deliberately to reveal possible mucosal anomalies.

CONCLUSIONS

1. Roentgenographic studies of the mucosal aspect of the colon in colitis may reveal definite anomalies.

2. These abnormalities are more or less distinctive in simple chronic colitis and in ulcerative colitis, to one familiar with their interpretation.

3. The elasticity of the colon wall would appear to be impaired in simple chronic colitis. In patients with such affections, the colon may become dilated and may exhibit areas incapable of contracting in the normal fashion.

4. Study of the degree and rate of contractibility of the colon may permit an appreciation of why clinically, the subject may quickly experience constipation or diarrhea.

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SECTION VII—*Surgery of the Lower Colon and Rectum*

A New Sigmoid Cannula*

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THE object of this report is to describe a new sigmoid cannula which has been useful for aspirating mucus and for washing the bowel mucosa with tepid normal saline through the sigmoidoscope. The mucus and washings, thus obtained, have been used particularly for the identification of amebae, and generally for culture of the bacterial flora and cytological examination of the bowel exudates.

The cannula, (Fig. 1), constructed of nickel silver, is 16.25 inches long and has a uniform bore of 0.064 inches. The outside diameter is 0.100 inches. The proximal 2.5 inches of the cannula is bent at an angle of approximately 135 degrees so that the examining hand is thrown out of the line of vision, thus making it possible to inspect the bowel wall through the sigmoidoscope. A Luer lock at one end permits the attachment of a standard Luer syringe for aspirating mucus or washings. The terminal end of the cannula is dilated into a bulb having a diameter of 0.233 inches. This metallic ball acts as a guide and prevents possible perforation of the bowel wall.

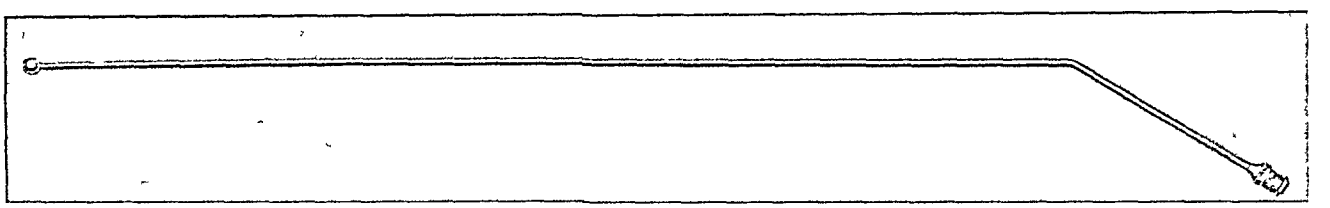


Fig. 1. Author's new sigmoid cannula.

Sigmoidoscopy is done one and one-half hours to two hours after the colonic irrigation or saline enemas. This allows sufficient time for any congestion due to the irrigation to subside and for any mucus higher up in the bowel to come down and be available for aspiration.

Following the passage of the sigmoidoscope to the region of the internal sphincter, the mucosa of that area is observed. At no time should it be necessary to use force in order to pass the sigmoidoscope. If areas showing definite pathology appear in the field of vision, the instrument should not be passed any further than that point. Any spasm is suggestive of underlying pathology and that region should be carefully scrutinized. If the patient has been prepared properly, a satisfactory examination can be made of the bowel mucosa below the area of spasm. If mucus appears in the field of vision, this should be aspirated through the cannula.

An important procedure is to irrigate the congested, edematous and ulcerated mucosa with tepid normal saline through the cannula. The saline wash is aspirated and set aside in a tepid bath for examination. The advantage of irrigating the bowel wall is that all the ulcers even those microscopic in size and regions infested but not yet broken down yield amebae and bacteria which are carried down in the saline suspension. As compared with attempted swabbing this has distinctive advantage in that the amebae are in warm saline suspension, free from the cotton of the applicator. The fields contain only cellular material and amebae. The motility of the amebae is unimpaired, thus making accurate diagnosis possible. In case of marked spasm, irrigation of the bowel wall with tepid normal saline has caused sufficient relaxation to allow easy passage of the sigmoidoscope with a minimum discomfort to the patient. Inflamed areas appear less congested following irrigation with normal saline.

The best results were obtained when specimens were *examined immediately after being secured*, since amebae tend to show degenerative changes rather early and disappear in about half an hour. When examined immediately after aspiration motile forms of amebae are found. Fresh unstained smears of mucus in saline should be examined as well as smears stained in iodine in order to differentiate any suspicious cells. Preparations fixed in Schaudinn's fluid and stained with iron-hematoxylin (Heidenhain's technic) are es-

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The author wishes to thank the American Cystoscope Makers, Inc., New York, N. Y., for their cooperation in the development of this instrument.

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Submitted June 3, 1936.

sential in order to confirm the diagnosis and to serve as permanent records of the cases.

The study of mucus specimens gave negative results in all patients in whom the clinical symptoms were not suggestive of amebiasis and in whom sigmoidscopic examination revealed a normal bowel mucosa. As yet, no false positive results have been obtained.

CONCLUSIONS

1. A new cannula for aspirating mucus through the sigmoidoscope has been described.
2. An accurate diagnosis of amebiasis can be made by a study of mucus obtained from the bowel by aspiration with the sigmoid cannula through the sigmoidoscope.
3. Negative results were obtained in all patients whose clinical symptoms were not suggestive of amebiasis and in whom sigmoidoscopic examination revealed normal bowel mucosae. To date, no false positive results have been obtained.
4. The advantages of the procedure outlined are (a) a positive diagnosis can be made within a single day with the minimum expense and inconvenience to the patient, and (b) by means of this technic, the amebae are obtained directly from their place of origin, suspended in warm saline, thus allowing for free motility.
5. The advantages of this instrument are that it is cheap, light, easily handled, does not obstruct the view during sigmoidoscopy and makes it possible to get a specimen that could not otherwise be obtained.

Annual Abstracts of Proctologic Literature

(May, 1934-May, 1935) By CLEMENT L. MARTIN, M.D., Chicago, Illinois

The complete bibliography from which these Abstracts were made will be published in full in the Transactions of the American Proctologic Society, 1935.

NEOPLASMS

The relation of polyps to rectal cancer continues to be investigated. The most careful and worthy work in the last year with which I am familiar is that of *H. Westhues*. His book, "The Pathologico-anatomical Basis of Surgery for Rectal Carcinoma" is reviewed in the December issue of the American Journal of Digestive Diseases and Nutrition. Although I do not fully agree with his classification of polyps, his material is different from my own and his findings are supported by much data.

Bargen and Dixon report on uncommon tumors in the large intestine. They found reported in the literature fibroma, fibromyoma, fibromyxoma, fibromyxangioma, adenofibromyoma, fibroleiomyoma, myoma, adenomyoma, angioma, lipoma, cholesteotoma, paraffinoma, taratoma, glioma, dermoids, and cysts. They report a case of fibroma in the cecum and one of myosarcoma of the rectum. They advise surgical treatment in all these conditions.

Coccyxgeal dermoids are discussed by *Ferrari and Meyer-Burgdorff*. *Fletcher, Woltman and Adson* present a study of sacrococcygeal chordomas.

In his paper on rectal polyps *David* makes the points that a biopsy specimen from the base of the tumor is necessary, that the slightest evidence of ulceration or induration are suggestive of malignancy, and that pathologist must have a history and definite idea of the tumor's gross appearance and the proper section for a diagnosis.

Newton Smith concludes that rectal polyps are comparatively rare in infancy. When they do occur they seem to grow rapidly and should be removed.

Poston reports an acute intussusception caused by a lipoma in an adult. *McKinney's* paper epitomizes current concepts of colon neoplasms. *Kuru* reports a lymphosarcoma of the rectum. *Read* performed a successful colon resection in a five year old child for a solitary adenomatous polyp which had caused recurrent intussusception. In a case of my own not yet reported, a single adenoma 2x2½ cms. was excised from the upper sigmoid by colotomy. Recurrent partial obstruction but no intussusception preceded the operation. The child recovered.

In a case report by *Hughes-Jones* of enterogenous cyst, the etiology is discussed from the standpoint of the origin of the diverticulum and from the basis of sequestration. *Pattison* writes on 6 cases of malignant lymphoma. The localized type is of special interest to the surgeon.

Bowman describes a villous papilloma of the rectum with early malignancy, a rare benign tumor which undergoes malignant changes in 12 to 20% of cases. It should be removed when found. It has struck me that these papilloma resemble very closely intravesical papilloma.

PILONIDAL CYST

Twenty-one cases of pilonidal cyst were treated by *Ferguson*. After excision he used primary suture and had but one failure.

Oldham states he has had 100% cure in 19 cases of coccygeal sinus since 1933 by primary union following excision and suture with non-absorbable sutures.

Cattell excises the sinus after marking out a triangular flap. Excision is carried out, the flap mobilized and the wound sutured, closing the flap horizontally and longitudinally. My own experience with primary suture has convinced me that it has definite limitations. When once the incision becomes infected, as it very commonly does because of its site, the suture material acts as a foreign body to retain infection. Recurrence is perhaps more probable after primary union. As in any open granulating wound, a suspicious area may be curetted or excised; recurrences have been prevented in some of my own cases by careful post-operative observation. (See Transactions, 1934, Pilonidal Cyst, Rogers).

In a preliminary report of 6 cases examined by the Philadelphia post-graduate group in which pilonidal sinus or sinuses were injected with 5% methylene blue and X-rayed after Weeder's procedure; none of them showed communication with either sacrum or coccyx.

PRURITUS ANI

Hermance and Bacon in their contribution to Pierson's Cyclopedia of Medicine give a very concise description of the condition, the actual causes are briefly enumerated and accepted treatments given. Evaluating the treatments as they so well could have done would have helped the general practitioner but might have caused rejection of their copy in a cyclopedia.

Terrill writes as one who has cared for many cases of the disorder, he reviews the various theories and treatments and regards allergy as a factor in few cases and states "My opinion is that fully 90% of the cases that come to me are primarily of fungal origin, although many of them become secondarily infected with other organ-

isms." He advocates constant hot dressings of mercuric bichloride, 1-5000 in the acute stage, and the substitution of a milder solution or a powder if drug dermatitis develops; in the subacute or chronic state, an alcoholic solution of red iodide of mercury.

The Philadelphia post-graduate group report on Gabriel's A.B.A. solution, nupercaine in oil, sterile distilled water, autogenous vaccine, and undercutting operations. We are fortunate to have such reports available. A cure has not been found. The "Resume of Experimental Studies . . . ." by Bacon, should be read in full.

FISTULA IN ANO

N. D. Smith advises delay in incising the abscess until there is definite fluctuation: "incision is indicated as soon as the abscess points or when there is definite superficial fluctuation." *Many may not agree with this view.* He states that a common practice, that of inserting gauze-strip packing is painful and of doubtful value; on this there will be more general agreement.

Murdoch saves as much as possible of the external sphincter where the fistulous tract crosses it. "Several years ago I began saving the continuity of considerable sphincter muscle at the site of fistulectomy. A slight amount of freeing of the bowel wall above is done. It is then possible to place the sphincter upward and stitch the rectal wall downward over it fixing the sphincter against solid tissue in a somewhat higher but nevertheless good functioning position. The final result is a more normal anal contour without as much notched defect, this is sometimes marked after the usual operation."

This technic was applicable to about 40% of his cases, in the others the usual fistulectomy is performed.

Allen and Haskell used a two-stage fistulectomy in 119 of 226 cases. This is extending a sometimes necessary procedure beyond what most proctologists will regard as its indication.

FISSURE, PAPILLITIS AND PECTENOSIS

Morgan reports 83 cases, which he operated, whose lesions could be explained by the presence of pectenosis and a pecten band. He concludes that pectenotomy is the method of choice and advises against the practice of divulsion in dealing with this condition.

The Philadelphia post-graduate group treated 4 cases of fissure by injection of Gabriel's A.B.A. solution; it proved painful and unsatisfactory in these few cases. One c.c. quinine and urea hydrochloride injections fared little better in three other cases. Using smaller amounts, others have found them quite satisfactory in subacute small fissures. "Three fissures located in the posterior site were excised, after which the technic as outlined by Buie, namely, suturing the anal margin to the external sphincter muscle with catgut, was utilized. *All three cases* were followed by infection, and in one the sutures sloughed off."

INJURIES

Nightingale had a case of rupture of the sigmoid from compressed air. Unlike most of the cases, the nozzle of the air hose was not brought in contact with the anus by a practical joker. The workman was using the air to clean his clothes and accidentally touched the anus. There were several tears of bowel wall to but none through the serosa. Recovery followed laparotomy and repair of the bowel.

Black and *Weisman* in 1926 reported 27 cases, 19 of them fatal.

La Croix and *Ryan* cite the case of a farmer who suffered a common cause of rectal injury—that of impalement. This man slid down a load of hay causing the pitchfork handle, about 2 inches in diameter, to enter and lacerate the anus, rectum and sigmoid. The handle entered the bowel to a distance of 14 inches. He removed it himself. At operation a 6 inch rent in the sigmoid was found, most of the tear being in the mucosa, a relatively small portion through the serosa; a 3 inch laceration in the mesocolon was present. Recovery followed.

Epstein attended at the Lincoln Hospital a man who had inserted two apples in the rectum and who had at various times previously used a cucumber and parsnip in the same manner. On entry the patient had a 2 inch tear in the recto-sigmoid, localized peritonitis, and free soapsuds in the abdomen. Trauma from efforts at removal and a soapsuds enema explained these. The tear in the recto-sigmoid was not seen proctoscopically although the instrument was passed beyond its site. The star shaped appearance at the center of the apple, as seen in the roentgenogram, was a point of interest. The patient recovered.

INFLAMMATIONS

Several articles reveal the importance of the colon and rectum as foci infection. *Hirschmann's* discussion of the subject is definitely informative.

An unusual type of chronic buccal and peri-anal ulceration is described by *Wiseman* in which diagnosis was impossible and therapy of little avail. *Preusser* emphasizes the importance of anal infection in an article treating of the general phases of the subject.

SECTION VIII—*Editorial*

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastro-enterological Association is in no way responsible for editorial expressions.

CONCERNING THE ENIGMA, PEPTIC ULCER

I.

DURING the past three decades, considerable of the basic pathology of peptic ulcer has been established. Along broad lines, the effects of ulcer presence upon gastric and duodenal physiology now are appreciated. Physiologico-chemic investigations, conducted relatively recently, promise to cast light upon hitherto suspected, but not substantiated, phenomena concerned with the secretory and motor interdependence of the stomach, duodenum, the upper small bowel and biliary tract segments, and on the biochemic significance of "end" products of digestion in regard to a regulatory mechanism for digestive juice production, motor sequences and absorption in the presence or absence of peptic ulcer. In some aspects, these studies appear even to carry pointings with respect ulcer etiology and persistence. Experimental surgery, conducted under purposeful planning, has returned information of great worth as to what pathologic and physiologic deviations appear when anatomic disruptions deliberately are brought about and when, in the upper digestive tract particularly, the orderly, consecutive processes of food reception, digestion and absorption are interfered with. Studies of this character have raised a veritable mountain of facts, pathologic chemic,

motor, secretory, metabolic, nutritional, some of which appear to have bearing upon ulcer production or, its maintainence.

But, although facts have accumulated, there still exists much puzzlement as to how the majority of these facts is to be interpreted; particularly, what they mean, for example, in respect peptic ulcer. What do these facts signify apart from revealing how readily may develop stomach, duodenal and small bowel lesions of ulcerative kind, when foreign tissues are joined one with another; when secretions normal to one viscus are introduced into those to which they are strange and when such secretions perform no regular physiologic function; when nerves, blood vessels or muscles are forced to perform in uncoordinated or non-related fashion (anatomically and physiologically)—and so on? There are no limits to the speculative hypotheses which may be set up or to the fashion in which observed facts may be grouped and interpreted. Certainly, few of the experimental surgical procedures which result in peptic ulcer production or persistence or again, which prevent the development or initiate healing of ulcerations produced in the presence of disorganized anatomy, physiology or metabolism, basically seem to mean (even under the most liberal interpretations), little more than (*a*) evidence of how necessary it is in animals or man that anatomic integrity be preserved if normal function is to be expected, (*b*) how great may be the insult to normal structural *schemata* before there arise abnormal physiologic or biologic tissue departures, (*c*) how constant and strenuous are the efforts of disrupted anatomy and chemistry to adapt themselves to structural defects and to attempt to perform their normal work despite the serious handicaps imposed and *(d)* how, only in the presence of most radical anatomic maladjustments (*e.g.*—anastomosis of terminal ileum with the stomach; the "Mann-Williamson preparation," etc.), can functional disorganization be so profound as to overwhelm "natural" adaptability and so cause fatal issue. One marvels not so much that experimental surgery, as conducted, may cause visceral ulceration or that, when such ulcers have arisen, "substitution" structural arrangements or exhibited therapy may heal or, if instituted in time, prevent them, but that animals or man are endowed with such reserve digestive and absorptive mechanisms that permit injury (in the broad meaning) of a degree fundamentally almost opposite to that normal to the subjects, before pathology supervenes, digestive sequences are not carried forward sufficient for basic nutritional needs and *exitus* follows! It is well to recall that, in most instances, experimental surgery is being exhibited to animals which in their normal life-course, are not affected with peptic ulcer as one observes it in man: namely, a *spontaneously* arising lesion, which selects its own location, is grossly overwhelmingly "solitary" in incidence, is non-inflammatory, may or may not give rise to symptoms, or, until such complications, as the scar of healing, hemorrhage or perforation, may interfere but little with general nutrition or (provided the patient thinks he has but "dyspepsia" and is not gravely concerned by the knowledge that so "dread a disease as ulcer is gnawing at his vitals") with economic efficiency!

Thus, as to cause and not a little, as to effects, to internists and surgeons generally, and even to those internists—gastro-enterologists—who have acquired special knowledge of digestive tract disease, peptic ulcer still persists as a baffling enigma, clinically and, particularly, therapeutically. To those most familiar with factual data, the "ulcer problem" still is unsolved. Only individuals possessed of superficial or ancient knowledge, second-hand facts, the single-track mentality which finds comfort in set formulae and particularly, therapeutic regimens to which patients are fitted irrespective of their individual pathology or symptomatology—only to such readily satisfied persons does gastro-duodenal ulcer occupy any sort of satisfactory status.

To the experienced clinician, not the least distressing aspect of peptic ulcer is that which deals with its therapy. Inasmuch as comparatively little is accepted by those who are informed concerning the etiology of the lesion and since each subject's peptic ulcer is an individualized affection (as to position, size, histologic kind, tissue damage, secondary pathology, chemic effects) one must realize at present, that any "ulcer" *treatment can be only empiric. Actually, our "modern"* therapy is nothing more distinctive or positive than an attempt to relieve symptoms, to protect known or suspected damaged mucosa from dietetic and, vaguely, chemical traumata, to correct faulty visceral motility, to improve the patient's capacity for tissue repair by bolstering general nutrition and, when histo-pathologic complications menace life, to perform surgery appropriate to the special demands. However professionally distressing this admission may be, solid progress in peptic ulcer treatment will not be possible until the mechanism of ulcer production truly is established and universally admitted, the "life history" of the lesion recognized, its pathologic variations appreciated and the mass of therapeutic rubbish, accumulated on slim foundation during the past sixty years and now spread broadly on the pages of so-called "standard" text books, swept into final discard. Clear clinical thinking must replace dogmatic opinion, the exhibition of what is therapeutically curious or novel, faddism, the memorized formulae of student sophomorism and the pernicious practice of fitting ulcer subjects to *schemata* of "hand-me-down" diets and drugs which have descended from the days of Celsus *(De Medicina: "ad hibendi lenes et glutinosi sed citra solietatem: omnia acria atque acida removendi; vino utendum, sed neque procfrigido neque nemis calido").* As the therapeutic situation now stands, patients and physicians are lulled into a degree of smugness wholly unwarranted by facts. Certainly, at present, one can speak of "cure" only in its Continental significance of *"Kur"*: a *method of management* and *not a positive therapy* whereby restoration of normal visceral structure and function fairly definitely follows specific, directed effort.

So chaotic are the conceptions for and practices of peptic ulcer management, (particularly when one recalls that few lesions have so intensively engaged the efforts of so many investigators and clinicians for the past thirty years), that, at this late date and from a clinic whose experience doubtless exceeds that of any, one who has been veritably steeped in the ulcer problem now comes forward with what may be interpreted as a "where are we?" attempt at appraising today's ulcer therapy.*

*Andrew B. Rivers, M.D.—"A Consideration of Some of the Newer Methods for the Treatment of Peptic Ulcer," Mayo Clinic Read at the 29th Annual Session of the American Gastroenterological Association, May 4-5, 1926.

We are not acquainted with the kind of approach to the problem contemplated by Dr. Rivers but we believe it to be not out of line here to call attention to some aspects of peptic ulcer and its treatment which warrant consideration.

II.

(1) *What is it that is to be treated?* Most non-surgical "treatments" still are devised and exhibited on the theory that the "peptic" lesion is *gastric* and, that faulty gastric chemism requires correction if ulcers are to be placed in an environment most conducive to healing. In fact, the majority of standard text-books emphatically give the impression that gastric ulcer is the more frequent and the more important lesion. All clinical, surgical and post-mortem data prove that the duodenal lesion is of incidence to *the gastric anywhere from 3 to 1 to 6 to 1 depending* upon modes of classification and whose statistics are studied. If Mayo's anatomic definition of where the stomach ends and the duodenum begins, is accepted, then there is a ratio of four duodenal ulcers to one gastric. Despite this observation, in the vast majority of instances, the clinical mind still thinks in terms of the gastric lesion when non-surgical ulcer therapy is to be employed and, almost universally, the treatment regimen basically is arranged so that, theoretically, conditions favor the healing of a stomach defect *which includes a mucosal lesion of ulcer kind.*

These commonly exhibited modes of therapy are directed towards the protection or the healing of what is regarded as an open, "raw" mucosal area. Such "protection" is to be accomplished by "smooth" diet, or by drugs presumably which *select* and *adhere* to the "raw" surface and thus defend it from chemical or food trauma. Under this "protection-coat," spontaneous or medicinally stimulated mucosal repair is assumed to occur. Of the drugs employed, bismuth, gelatinous substances, aluminum or mucins are most favored. In association with such "protectants," various alkalies are given so that the "gastric juice" may be "neutralized" and hence its "corrosive" action upon the "raw" ulcer (even though such already may be covered by protective agents!) may be eliminated. In the majority of "ulcer regimes" proposed, a chief objective lies in bringing *gastric* chemism to a *neutrality* (so far as free HCl is concerned) even though clinical, operative and post-mortem studies disclose that duodenal ulcer is at least four times as prevalent as is gastric and few data are available regarding the free HCl in the duodenal content, with or without admixture of bile, pancreatic juice and *succus entericus.* Incidentally, it should be remembered that could one succeed in keeping a stomach without free HCl and thus preventing the action of pepsin, stomach digestion of the exhibited diet of milk, cream and eggs could not possibly occur: the chyme which then passes into the duodenum is not normal chyme but (apart from digestion of starch) is but an unsplit protein and fat food mixture which must depend for its digestion upon digestive agents distal to the pylorus. Duodenal contents lag but briefly in that gut segment, as Roentgen studies show, provided there is no organic obstruction or local ileus. Hence, if free HCl is neutralized *in the stomach, and eggs, milk, cream,* etc., are fed, the digestive burden falls largely upon the jejunum. Often has it been shown that severe local or general injury to the stomach's mucosa heals rapidly in the presence of high free HCl and pepsin.

Let us examine several of the above hypothesis upon which, in the vast majority of instances, peptic ulcer therapy depends and statistics relative cure are accumulated. *First,* as to the "open" or "raw" *mucosal defect* so commonly visualized by physician and patient alike, what are the facts?

In our own records, of 61 uncomplicated (non-stenosing, grossly bleeding or acutely perforating) gastric ulcers which came to operation at the height of digestive pain and discomfort, *11 only revealed non-epithelialization of their edges and bases. Fifty gastric ulcers* (quite as painful as the 11 above mentioned) *exhibited complete mucosal integrity; in fact, 33 of these "ulcers" (66%) actually were mural placques composed of well-delimited scars of various sizes and thicknesses.* Of these 33 lesions, 15 were so deeply mural as to present "soldier-spot" like scars on the peritoneal coat; another 4 "ulcers" had *"penetrated" through all the stomach wall coats* but complete perforation had been prevented by serosal scar plus reinforcement by the pancreas or the omentum. Such evidence at once imposes the conclusion not alone that with comparative rarity does peptic gastric ulcer present the "raw" mucosal surface which demands "protective" agents or calls for drugs or diet "neutralization" of free HCl and the consequent nullification of peptic activity, but emphasizes the very important fact that the great majority of peptic gastric "ulcers" is not "ulcer" as commonly understood, but is a *mural lesion* which, depending upon its extension towards the mucosa, may be or may not be complicated by such epithelial destruction as to give rise to a secondary ulcer-type lesion on its lumenal aspect. However, all evidence, histopathologically, indicates that the *initial lesion definitely is a wall defect;* the mucosal changes which have given it the name "ulcer" are nothing more than complications dependent upon factors which determine extension of the lesion so as to include that mucosa. Such complications may owe their occurrence to the fact that the tissues from the initial mural lesion towards the mucosa are less dense or resistant than are those towards the serosa, their blood vessels, being "terminal," most readily are occluded or destroyed; once such has happened, the resultant mural structures mucosalward die; they are digested by *any* proteolytic agent which may be present in the stomach's lumen and an ulcer-form *facade* is given to the primary mural lesion. Study of the initial mural defect whose extension towards the visceral lumen does *not* result in "ulcer," reveals that its progression towards the serosa is of a nature precisely like that which takes place when the extension includes the mucosa, but although in that progression, mural structures wholly may be destroyed, no "ulcer" complication is exhibited at the serosal limits unless complete perforation of the serosal wall occurs. One then has a "through and through" non-inflammatory "ulcer" which, when once it has arisen, makes difficult the opinion as to whether one is to lay greater emphasis upon mucosal than upon mural and serosal tissue loss. However, one may say that the "perforation" (when partial and not in association with a through and through lesion, *i.e.* the mucosal "ulcer"), is less serious than is that occurring when the initial mural defect breaks through the serosa and is not protected by peritoneal or omental

scar or backed up by such solid organ as the pancreas or the liver.

It is of the greatest interest to note that, while in our series of 61 operatively demonstrated gastric lesions, in 19, mucosal reparative integrity was adequate; the initial mural defect had extended as mural scar through, to, and including the serosa ("soldier-spot" lesion) in 15, and through even the serosa ("protected" perforation) in an additional 4. In all these 19 instances, the stomach wall had been preserved *in-so-far as preventing the passage of gastric contents* through it, but in each case, a through and through sterile or infected wedge of scar-tissue had replaced normal mural structures. Areolar tissue, glands, lymphatics, blood vessels, muscle layers, serosa had been destroyed and in their places there had been interposed a block of scar tissue. This wedge of scar locally, but seriously, interferred with coordinated neuromuscular functioning of the stomach, in degrees depending upon size and location. The location and the size of the wedge of scar could not fail to affect both secretory and motor activity, to a degree proportional with its destruction of normal structures. It would seem that motor interference is of great significance inasmuch as relatively few (9%) of the mural defects, whether or not bearing the mucosal ulcer-complication are located in segments of the stomach which have to do with the elaboration and excretion of free HCl. Since most of these scar wedges are located along the lesser curve, in the antrum or the pyloric section of the stomach, even wedges of but a centimeter or so would seem capable of interfering seriously with the intricately complex, criss-crossing and interweaving layers of muscle, richly supplied with nerves, which combine to form the structure of these gastric segments: segments which not alone are vigorously concerned with chymification but which actually differentiate so specially as to form the pyloric "ring."

(To be continued)

Frank Smithies

SECTION XII—"*The Clinic*"

Chronic Appendicitis

By

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IT is true that the appendix has many times been removed unnecessarily; that frequently it has been charged with producing symptoms for which it was in no way responsible; that repeatedly it has been wrongly accused by the physician or surgeon who hastily attributed to it disturbances of health which it did not cause and which its removal did not relieve. Thus the diagnosis "chronic appendicitis" has rightly come to be discredited and looked upon with more or less suspicion. Nevertheless the fact remains that in many instances chronic appendicitis affords the true explanation for certain chronic disturbances of gastric or intestinal function. Furthermore with care such cases can be identified with certainty and relieved by surgery, after dietetic and medicinal measures have all failed. A case recently observed has served to call attention anew to this situation.

A woman, aged 48, complained of distress after eating, with accumulation of gas relieved by belching it and passing it by bowel. For years past she had been constipated and her bowels rarely moved without assistance. She had to take a laxative every night and supplement this by an enema every day to secure a regular and satisfactory evacuation. Some years previous she had attacks of pain in the bowels, which she designated "colicky spells," occurring every few weeks; but more recently less often because of her routine of laxatives and enemata. Such attacks never lasted over one day and were not accompanied by fever. She observed no soreness or tenderness of the abdomen as a rule, except when her attacks of colic recurred.

This patient was small, pale, poorly nourished; but gave no evidence of organic disease anywhere in her body except in her abdomen. There tenderness was found over the right lower quadrant and a doughy mass, with muscle spasm but no definite tumor.

Laboratory examinations gave no evidence to elucidate her condition; but the explanation finally was supplied by an X-ray film of the colon after a barium enema. This showed the cecum dilated and low, hanging over the brim of the pelvis, with the appendix behind and below it. Both the cecum and the low retrocecal appendix were tender on palpation. The terminal ileum could not be made to fill at any time during the examination.

At operation the cecum was found covered by a Jackssonian membrane. The appendix showed signs of old inflammation and was somewhat distorted by bands of adhesions which were attached near its middle and to the retrocecal wall. It was swollen, firm and rather pale. Even more important was the presence of a sharp kink of the terminal ileum within the last 10 cm. above the ileocecal valve. The bowel there was folded upon itself and adherent for a distance of about 3 cm., the adhesions involving not only the wall of the bowel but the mesentery as well. The appendix was removed, the kinked bowel released and straightened and the mesentery freed. The patient had been told elsewhere before coming to San Francisco from her home in the country, that a diseased gall bladder was the probable cause of her symptoms, be-

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cause the X-ray shadow after the dye was faint. But exploration of this organ with the abdomen open showed it perfectly normal in color, thickness and consistence. The patient made a rapid recovery and has remained free from her former discomforts ever since.

In this patient the outstanding symptoms were those of disturbed intestinal function. But in others such an adherent, deformed appendix may reflexly disturb gastric functions more than intestinal, either increasing secretion so that the picture resembles that of ulcer; or impairing both secretion and motility to such an extent that chronic gastritis with atony is closely imitated. In still another group gastric secretion may be found within normal limits in spite of the patients' complaints. Again, physical examination throws little or no light on the problem; gastric analysis may prove that secretion is abnormal but does not tell why; and fluoroscopy and X-ray films are necessary in order to demonstrate where the real trouble lies. The barium meal serves to eliminate ulcer or other organic change in the stomach and duodenum; but it requires a barium enema to prove with certainty the presence of abnormalities in the region of the cecum and appendix upon which the symptoms depend. These abnormalities comprise delay in the terminal ileum after the barium meal or its entire failure to fill after the barium enema; fixation of the cecum, tenderness over the inner side, cecal stasis and delay in its emptying time. The appendix itself may or may not be visualized. If visible it may be fixed and tender, unusual in shape and size, kinked or angulated or beaded or clubbed. Frequently it is slow in emptying, retaining barium for 48 to 72 hours or even longer. If the appendix is not visible, the absence of such signs in the X-ray films does not prove that it is normal, for it may be adherent behind the cecum and thus obscured by opaque material in the bowel, or its lumen may be obstructed so that barium can not enter; or it may be obliterated, atrophic or buried by adhesions. The following case is typical of the group now under consideration.

A man, aged 42, had for five or six years suffered from "stomach trouble" previously diagnosed as chronic duodenal ulcer. The symptoms had been recurring attacks of pain in the epigastrium, belching, water-brash, burning, nausea and vomiting, appearing one hour or two after meals, lasting for weeks at a time. Such attacks never entirely disappeared, even on routine treatment for ulcer, but would grow much less annoying for varying periods of remission. At the time he sought advice, he had no such pain, nausea or vomiting as described but complained of a heavy, dragging feeling in the pit of the stomach after every meal. No signs were found on physical examination over the upper abdomen but decided tenderness and a palpable finger-shaped mass in the appendix area. Gastric analysis demonstrated a high-grade hypersecretion, with total acidity 84 and free HCl 72. But X-ray films discovered no defect in stomach or duodenum, while they did show the cecum fixed, with the appendix indistinctly outlined and tender to pressure. After six months observation and treatment by diet and drugs the patient was no better; so operation was advised. When the abdomen was opened, a fibrous band was found extending from the base of the cecum to the abdominal wall; the cecum was twisted upon its axis and bound down to the wall of the pelvis by old inflammatory adhesions; the appendix was buried behind the cecum by adhesions that fixed it throughout its length. All adhesions and constricting bands were freed and the appendix removed. Five years have elapsed since that operation during which the patient has had no recurrence of his former attacks and has remained free from all gastric disturbances.

These illustrative case histories of chronic appendicitis could be multiplied many times from the written records of patients seen during the past 30 years. But the object is simply to call attention anew to the fact that chronic indigestion is frequently the consequence of old long-standing pathology in the region of the cecum and appendix produced by one or by several previous attacks or subacute inflammation involving these parts. Haste in reaching this conclusion, however, is most deplorable and has been the cause of numerous errors in the past.

The evidence which makes this diagnosis probable is first, a history of persistent disturbance of gastric or intestinal function or of both; but there is no history that is diagnostic and many variations occur. There may be mixed up with the digestive symptoms as account of more or less constant soreness and tenderness in the right lower quadrant and dull pain there at times, but this is not at all essential. Intercurrent attacks of cramps with diarrhea may form a part also of the clinical picture. From history alone, however, no conclusion can ever properly be reached. Physical examination likewise is untrustworthy. The signs it reveals are often vague and indefinite and may not be noted at all. They may be obvious at one examination and not discovered at all at another. Gastric analysis is variable in its results, inconclusive and never diagnostic; but of value because it aids in excluding organic gastric disease. Of all methods of investigation, X-ray examination is of the greatest value in chronic appendicitis, particularly after a barium enema; but even this may not always show the changes previously described to an extent that make them conclusive. It is only by combining the various items of evidence acquired that a trustworthy conclusion can ultimately be reached. Even so, in any obscure case, where manifestations are not urgent and delay does not imperil life, it is better to proceed slowly before advising surgery and to await developments while the patient is kept under observation, with dietetic and medicinal treatment calculated to relieve symptoms even though it does not modify pathology.

Post-Operative Hemorrhage Following Acute Ruptured Pre-pyloric Ulcer

By

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A FAIRLY thorough search of the American and foreign literature has failed to show any exhaustive articles on this subject. We have reviewed many papers devoted to post-operative complications following gastric surgery but no mention has been found regarding this condition. It is taken for granted, therefore, that this case of our's is an extremely rare one, and in view of its unusual features and the fact that the patient survived, it is reported in detail.

CASE REPORT

W. D., 26 years of age, a baggage reporter, was admitted to the Columbus Hospital Extension on April 24th, 1935, at 2 a.m., with a typical history of ruptured ulcer; sudden onset of pain four hours previously, slight vomiting, boardlike rigidity and tenderness of the abdomen. He stated that he had had gastric trouble for four or five years. He was fairly robust and had a good color.

Three hours after admission and eight hours after onset of symptoms he was operated on by Doctor Alvich, who found a calloused, prepyloric ulcer on the anterior wall of the stomach with a perforation about one-half inch in diameter; the peritoneal cavity was filled with gastric content. This was evacuated and the perforation closed by two purse-string, chromic sutures and a tab of omentum sutured over this area. A cigarette drain from the subhepatic space was brought out through a stab wound to the right side of the operative wound. The incision was closed in layers with silkworm for the skin.

During the first postoperative week the patient ran a slightly elevated temperature in the afternoon, sometimes as high as 101°, but his pulse rate stayed between 100 and 110. He was allowed to take liquids gradually and seemed to be in fair shape.

Then, on *April 29th*, there was some serous discharge from the incision and three sutures were removed. The following day he was unusually pale, and a note was made that there might be hemorrhage in the gastro-intestinal tract. The red blood cell count was then 1,800,000, and the hemoglobin 40%. Stool examination the next day showed strongly positive reaction for blood. A transfusion of 500 c.c. whole blood was given. On May 4th, the stool was still positive for blood and most of the wound had disrupted, being kept together only by adhesive.

On May 6th, the hemoglobin was 40% and the red blood cells numbered 3,320,000. *On May 10th*, the hemoglobin was unchanged but the red blood cells had dropped to 1,700,000. Another transfusion of 570 c.c. of whole blood was given on May 11. Two days later a third transfusion of like amount was given. The following day, the hemoglobin was 60%, and the red blood cells numbered 3,130,000. *On May 16th*, the fourth transfusion was given, this comprising 710 c.c. of whole blood.

Throughout this period of 16 days, every means was employed to stop the bleeding. Sodium citrate was given intramuscularly, as well as clyses, liver extract and even glucose, 50% solution, by mouth. The stools persistently showed strong positive reactions for blood despite these measures. The patient continued to vomit and was considered to be in poor shape.

It was decided, after consultation with the radiologist, Doctor Massaro, to attempt to localize the ulcer, if possible, by *Roentgenologic study*. A special preparation of barium mixture was given by mouth, in small quantities, and the patient was fluoroscoped for some time. The barium mixture was found to remain in the stomach except a small amount that entered the duodenal bulb. This appeared markedly narrowed and had the appearance of a small crater in the wall. After two hours the barium was still in the stomach.

Second operation: Despite the fact that the original incision had disrupted, it was felt that another laparotomy was indicated in order to save the patient. Therefore, on May 17, he was again explored through a midline incision, under gas oxygen anesthesia.

The disrupted wound had as a part of its base the anterior surface of the pyloric end of the stomach. This had to be freed in order to expose the right side of the abdomen; much of oozing resulted in doing so. The duodenum and pylorus were matted together in a mass of soft adhesions up against the inferior surface of the liver, and it was impossible to expose freely the duodenal area. We felt that the only procedure was to ligate the pyloric end of the stomach; this was done with a double silk ligature. A posterior gastro-enterostomy was performed, fairly easily, and a patchwork repair of the two abdominal incisions was made with through-and-through, interlocking silkworm gut sutures. The patient was then given repeated infusions of glucose in saline together with 100 c.c. of alcohol for every 1000 c.c. of solution.

The following day the temperature rose to 101°, the pulse to 150, but these dropped to 101° and 100, respectively, next day. From then on improvement was steady. The abdominal wound healed with very little discharge. There was very little distention and by May 25, eight days after the second laparotomy, there was only a trace of blood in the stools.

Then, however, the patient developed an *acute parotitis* on the left side. In spite of all applications, masticatics, massage and the like, the swelling increased. Although there was some discharge from the left auditory canal, an *incision had to be made in the left parotid gland on May 31;* a large amount of pus was evacuated; this on culture showed staphylococci. From the time of the incision of the parotid, improvement was steady; all wounds healed nicely, the patient ate more and more varied foods, and left the hospital two months after his initial admission.

Follow-up examination at the end of September showed a gain of 30 pounds in weight, the patient was eating nearly all solid foods without discomfort, and his abdominal wall exhibited but weakness between the two incisions.

DISCUSSION

In our opinion the facts that this patient had a disruption of his primary operative abdominal wound, had profuse, post-operative, gastric hemorrhage for at least 10 days, was able to withstand a second extensive exploration of the abdominal cavity, a posterior

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gastro-enterostomy in a contaminated field, and a suppurative parotitis, make this case truly unique.

The question of from whence the hemorrhage came, cannot be answered positively. At the time of the first operation no unusual bleeding was noted at the site of the ulcer perforation. At the second operation the duodenum and pylorus were matted together under the inferior surface of the liver and no strenuous attempt was made to separate them. The presumption is, however, that the bleeding came either from the sloughing margin of the original ulcer or from a point close by, as the patient never vomited blood; after ligation of the pyloric end of the stomach and gastro-enterostomy bleeding stopped.

Whether the closure of the pylorus with a double silk ligature was advisable is questionable. We felt, however, that the patient could not stand a resection and we felt also that a gastrojejunostomy alone would not stop the bleeding. As far as we have been able to determine, the patient now feels well, eats a varied diet and has no symptoms of indigestion or pain.

In the literature Berg (1), notes that, in cases of perforated peptic ulcer, multiple ulcers often occur. He reports two cases, both duodenal, which had a perforated and a bleeding ulcer at the same time. Bartrand (2), also cites two cases of severe gastric hemorrhage in the post-operative period following operation for perforated ulcer. One of these died; the autopsy showed a second ulcer on the lesser curvature, which was cicatrized, apparently not the source of the bleeding. In the other case, a secondary operation was done, gastro-pylorectomy; the patient recovered. An ulcer was found on examination of the portion resected, (not the perforated ulcer) but careful examination did not show any important arterial lesion in it. However, all gastric hemorrhages ceased after the second operation.

McCreery, in discussing this case, stated that in a series of 160 cases of acute perforation on his service at the Bellevue Hospital, the complication of severe, post-operative bleeding was encountered only twice. In the first case, the hemorrhage was so copious that the ulcer perforation was not recognized until it was located at autopsy. In the second case, the simultaneous occurrence of hemorrhage and perforation forced a delay of operation for six hours in an effort to get the patient in condition to stand laporatomy.

In conclusion, we would like to stress the fact that an apparently profuse hemorrhage may follow a perforated ulcer and it is only by close observation of the patient, his stools and by frequent blood studies that it may be recognized. With proper preoperative treatment, including especially the exhibition of frequent transfusions of whole blood, etc., a second laporatomy allowing extensive gastric surgery can be done even in a contaminated field.

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ABSTRACTS

NUTRITION

COSTELLO, JOS. P.

Obesity and Ocular Symptoms in Mentally Alert Children Due to Hypothyroidism. Endocrinology, Vol. 20, No. 1, 1936.

Many clinicians will recognize in this valuable contribution of Costello's a type of patient that they have seen in practice. The generally held opinion has been that in the presence of true hypothyroidism in children, obesity will always be associated with delayed bone development and mental torpor. In the type here described neither of these are found. In fact the patient, presenting a basal metabolic rate of from minus 14 to 26 is distinguished by her mental brightness and her interest in her environment and by some degree of ocular myopia. Dieting alone does not quickly reduce the weight or entirely fails to do so. Even with the administration of thyroid, results are very slow partly because large doses are badly tolerated and small doses over a long period of time are necessary. It is also to be noted that while thyroid greatly improves the weight and the visual defect it actually cures neither. In the few cases of Costello's syndrome which the reviewer has treated two other features were noticeable: excellent attempt at co-operation and a pathological proclivity to lying.

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HANES, F. M., HANSEN-PRUSS, O. C., EDWARDS, J. W.

The Feeding of Modified Gastric Juice in Pernicious Anemia. J. A. M. A., Vol. 106, pp. 2058-2059, June 13, 1936.

Greenspon recently offered an explanation of the role played by the gastric juice which was different from Castles' theory of the interaction of intrinsic and extrinsic factors.

Greenspon's experiments were recently repeated in five typical and untreated cases of pernicious anemia. His technic was adhered to throughout the experiments. The gastric juice used was taken from fifteen normal, healthy medical students, and histamine (0.1 mg. per kilogram body weight) was used to stimulate its flow.

The patients were all typical cases of pernicious anemia. They were all given large amounts of gastric juice (1750-2370) daily for a period of time varying from four to nine days. In one case the reticulocyte count went up to three per cent, while in the other cases it never went over one per cent. After the administration of liver extract there was the usual reticulocyte response with aleviation of symptoms.

From these results the conclusion was reached that modified gastric juice has no beneficial effect in pernicious anemia.

Francis D. Murphy, Milwaukee.

WAKEFIELD, E.E., AND ELLINGER, S. C.

Diet of the Bluff Dwellers of the Ozark Mountains and Its Skeletal Effects. Ann. Int. Med., IX, 1412, April, 1936.

This rather unique study was made on skeletons and parts of mummified bodies in the University of Kansas. The undigested food residue seen in the feces was studied with the hope of de-

anxious to end the test. The first seven protocols illustrate the various types of response obtained and are self explanatory. The results have been grouped together in the construction of the composite curve shown in Graph I.

It should be recalled that the average fasting secretion among normal persons is 20 c.c. or more per ten-minute period, according to Bloomfield (8). Our studies, on the whole, corroborate this statement. We have considered a secretory rate of less than 5 c.c. per ten-minute period as marked reduction in volume and a secretion above this figure but less than the fasting control figure as a moderate reduction in volume. Those cases in which the free acidity dropped to zero after the administration of the drug have been classed as a marked reduction in acidity regardless of its duration. Those cases in which the free acidity dropped below the previous fasting level but did not reach zero have been classed as a moderate reduction in acidity regardless of its duration. Those who showed only slight or indefinite changes were grouped under the headings of "No effect." Using these criteria our results are summarized again in the following table:

Summary of Results

	Volume (No. of cases)	Free Acidity (No. of cases)
Marked Reduction	20 (64.5%)	10 (32.2%)
Moderate Reduction	10 (32.2%)	7 (22.6%)
No Effect	1 (3.3%)	10 (32.2%)
Increased		4 (13.0%)
	31	31

From the results described, it seems that morphine in ordinary therapeutic dosage has a fairly uniform inhibitory effect on the gastric secretion in man under fasting conditions. The reduction of the volume of the basal secretion was more marked than that of the free acidity, although in one out of every three cases achlorhydria took place for sometime after the administration of morphine and in approximately half of the series there was a distinct lowering of the acidity in comparison with the fasting values.

That the very first specimen of the fasting stomach content usually does not represent the actual basal secretion is well illustrated in the protocols. Its volume as well as its acidity are easily affected by many factors, particularly in this series where most of the cases were ulcer patients. Attention is also called to the fact that the mere presence of a tube in the stomach seemed not infrequently to provoke some rise in the free acidity as shown in Graph II and some of the protocols. Should morphine be given right after the very first or second fasting specimen, one might very well be led to think that a brisk stimulation did take place at the beginning, as the depressing effect of the drug usually manifests itself only about 20 minutes after the medication.

The depressive effect of morphine on gastric secretion seemed to have a close relationship with the mental state of the patient. The more drowsy he became, usually the more marked was the depression. Those who became talkative or remain active after the medication gave the least response, and, in fact, occasionally a contrary effect.

From Graphs III, IV and V, it may be seen that morphine is not a strong inhibitor of gastric secretion. Its depressive effect could be readily over-shadowed by a new stimulus, whether it were a purely psychic one such as the taking of food by the patient in a neighbouring bed or a chemical one such as an injection of histamine. In the instances in which morphine seemed to act as a stimulant, the effect was a very weak one compared with that evoked by histamine or by a psychic stimulus.

The question of why morphine affects the volume of the basal secretion more than it does the free acidity is very interesting and one which we are not able to answer to our complete satisfaction. Keefer and Bloomfield (9) in 1926 and Porter (10) in 1931 observed the same phenomenon in their studies on the effect of atropine on gastric secretion.

DOG EXPERIMENTS

A series of experiments were carried out on two dogs with isolated stomach pouches. One of the two was a dog provided with a complete stomach pouch with an intact nerve and blood supply after the technic of Dragstedt (11), and the other with a classical Pavlov pouch. Morphine was used in 0.001 gm. doses, corresponding roughly in a 15 kg. dog to a therapeutic dose of 0.015 gm. in a 60 kg. human subject, but occasionally a bigger dose up to 0.012 gm. was also tried. No attempt was made to study the effect of larger amounts. The first dog was observed for a period of 45 days, and the second one for about 20 days.

The results obtained from these two dogs were quite inconsistent. Protocols VII and IX are illustrative of the variations observed under conditions as constant as we were able to maintain. Graphs VI and VII are composite curves representing the average values obtained. These are also summarized in the following table:

Complete pouch dog — *Pavlov dog*

	Vol. per 30 min.	Free HCl	Total acid	Times observed	Vol. per 30 min.	Free HCl	Total acid	Times observed
Basal	32	74	78	31	8	0	11	24
After morphine	17	126	122	24	11	71	82	17
After morphine	18	157	164	24	7	174	23	35

PROTOCOL I

Showing marked reduction in volume of gastric secretion in a case of duodenal ulcer after the administration of morphine. (Male, 52 years old)

Time	Amount	Free HCl	Total Acidity
10 min.	55	22	42
20	22	55	66
30	36	58	68
40	33	71	79
50	25	75	85
60	33	53	65
Morphine 0.01 gm.			
70	22	41	52
80	10	33	44
90	0		
100	0		
110	0		
120	0		
130	3	0	23

From the results shown above and elsewhere, it would appear that the dog does not react quite the same to a small dose of morphine as man. It was actually more difficult to control the surroundings of the dogs than it was those of the human patients. With the complete pouch dog, the control became a complicated problem. The constant loss of fluid and acid through the fistula, the necessity of feeding the animal several times daily instead of once a day as in normal dogs, the question of dehydration if starved too long,

PROTOCOL II

Showing moderate reduction in volume but with increased free acidity in a case of carcinoma of rectum with metastasis to the liver. (Male, 47 years old)

Time	Amount	Free HCl	Total Acidity
10 min.	40	3	16
20	48	14	26
30	28	12	22
40	36	32	42
Morphine 0.01 gm.			
50	21	36	45
60	24	34	43
70	23	0	6
80	7	0	10
90	2	13	30
100	9	20	40
110	11	44	54
120	10	43	55
130	5	50	62
140	18	26	42
150	5	30	47
160	3	30	41
170	7	35	47
180	8	35	46
190	3	47	58

PROTOCOL III

Showing no apparent reduction in volume nor any stimulating affect of morphine in a case of false achlorhydria. The low basal secretion is significant. (Male, 49 years old)

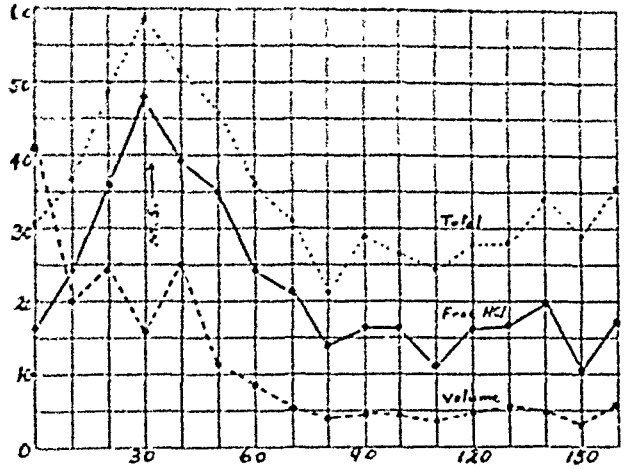
Time	Amount	Free HCl	Total Acidity
10 min.	11	0	7
20	13	7	18
Morphine 0.01 gm.			
30	28	0	11
40	13	0	12
50	4	0	12
60	14	0	17
70	7	0	16
80	7	0	14
90	10	0	17
100	4	0	15
110	12	3	18
Histamine 0.0005 gm.			
120	10	24	39
130	14	60	74
140	19	68	81
150	14	60	73
160	8	35	46
170	6	38	51

the amount of salt added to the food to replace the chloride loss, the psychic factor such as hunger and thirst—all seemed to be able to influence the results directly or indirectly. It was practically impossible to control the situation satisfactorily. The Pavlov dog, on the other hand, presented a much simpler problem since the greater portion of the stomach was intact. However, this dog was not altogether desirable for our purpose for it did not secrete enough fasting juice, and

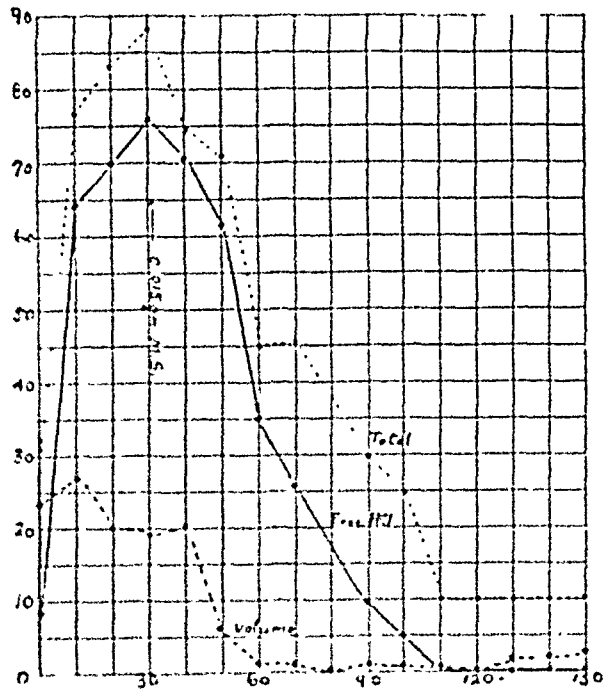
PROTOCOL IV

Showing marked reduction in acidity as well as volume in a case of duodenal ulcer. (Male, 33 years old)

Time	Amount	Free HCl	Total Acidity
10 min.	33	33	48
20	30	63	76
Morphine 0.01 gm.			
30	9	40	52
40	5	34	48
50	11	31	45
60	6	27	41
70	8	17	33
80	5	12	36
90	4	12	38
100	4	5	30
110	2	0	20
120	7	0	24
130	3	0	23
140	3	0	22
150	5	0	26



Graph 1. A composite curve showing the effect of morphine on the fasting gastric secretion in 31 patients.

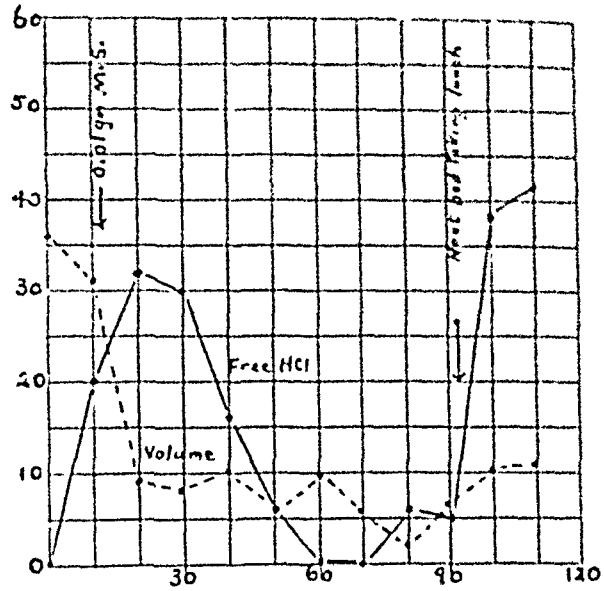


Graph 2. A typical curve showing the effect of morphine on gastric secretion in man.

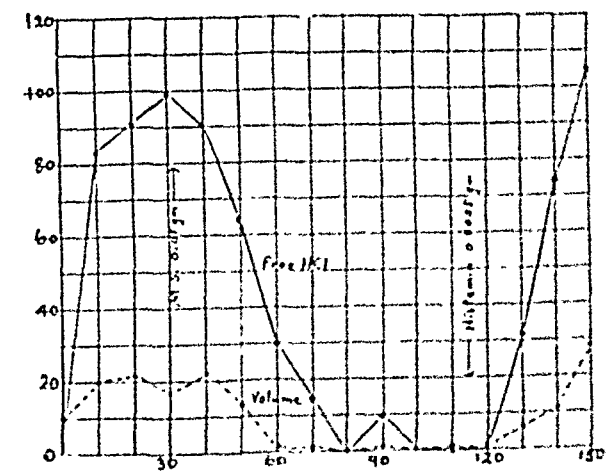
what is more, it did not secrete any free acid at all under the basal condition.

The operation for a complete pouch in dogs is a difficult one involving a very high mortality rate. The dog requires the most delicate post-operative care for a number of weeks before it sufficiently recovers from the operation and can be considered normal. In carrying out our experiments, attempts were made to make the conditions alike as far as possible, with particular attention to the time of feeding and the taking away of food and water at certain definite hours before the test experiment.

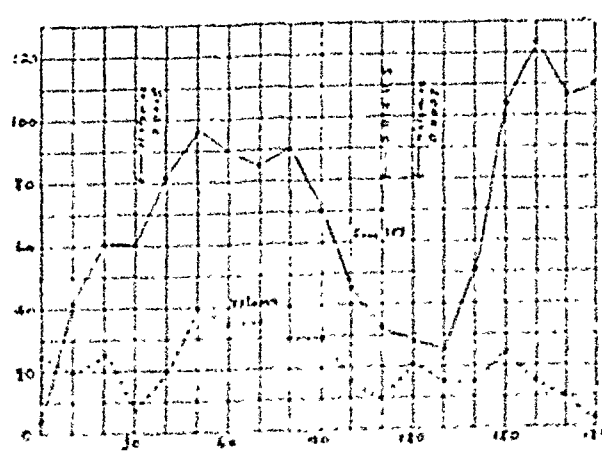
In spite of the precautions taken, the results obtained were very different. Even the fasting experiments varied considerably on different days. Since our observations do not represent an extensive study, it



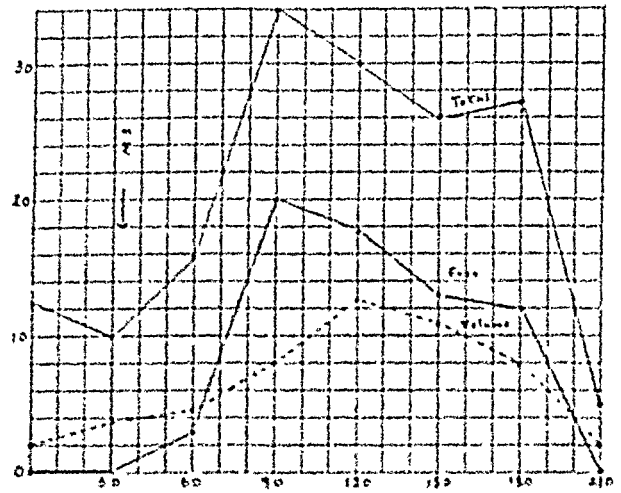
Graph 3. The influence of a psychic stimulus during the morphine inhibition period.



Graph 4. The effect of a chemical stimulus during the morphine inhibition.



Graph 5. The influence of morphine on gastric secretion when combined with histamine.



Graph 6. A composite curve showing the effect of morphine on gastric secretion in a dog with Pavlov's pouch. (Result of six tests).

seems best not to draw any positive or final conclusions from them. Nevertheless, it may be noted that the Pavlov dog showed a transient rise in volume and acidity after the injection of morphine on most occasions, while the complete pouch dog showed more inhibition than stimulation. The amount of stimulation in both dogs, however, was far less pronounced than those evoked by either food or histamine.

It is our impression that dogs are not entirely suitable for studying the subject in question, and the results obtained from them are not comparable with those obtained from human beings. The most obvious reason is that the dog and man do not react the same to morphine. A small dose of morphine readily causes a dog to become nauseated, and to vomit and defecate. There is a definite state of restlessness during the first

PROTOCOL V

Showing moderate reduction of free acidity with marked reduction in volume in a case with no organic disease. (Male, 26 years old)

Time	Amount	Free HCl	Total Acidity
10 min.	34	0	4
20	37	4	10
30	44	22	38
40	15	49	54
	Morphine 0.01 gm.		
50	12	54	62
60	9		
70	6		
80	4		
90	5	45	54
100	3	33	47
110	2	20	35
120	2	8	20
	Histamine 0.0001 gm.		
130	11	84	94
140	22	111	120
150	35	124	134

PROTOCOL VI

Showing no apparent effect on free acidity but with moderate reduction in volume in a case of duodenal ulcer. (Male, 37 years old)

Time	Amount	Free HCl	Total Acidity
10 min.	25	35	61
20	12	55	64
30	20	63	71
40	30	53	62
	Morphine 0.01 gm.		
50	30	45	55
60	4	57	62
70	7	43	60
80	8	56	63
90	10	33	45
100	2	15	25
110	15	51	59
120	5	66	72
130	3	55	75

hour or so after the administration. These are rarely observed in man.

The question of tolerance or addiction to the drug was also considered during our observations, although we tried not to give the drug regularly to the dogs. However, there was evidence to suggest that tolerance did play some part, as the dogs seemed to develop fewer symptoms with the same dose of morphine towards the later part of the period. The gastric secretions, nevertheless, showed no striking changes.

SUMMARY

Morphine in therapeutic dosage in man exhibited in the majority of instances an inhibitory effect on the fasting gastric secretion. Over 95% of the cases

PROTOCOL VII

Showing increased free acidity but marked reduction in volume in a case of duodenal ulcer with stenosis. (Male, 35 years old)

Time	Amount	Free HCl	Total Acidity
10 min.	70	0	4
20	22	4	6
30	35	21	44
40	21	45	56
	Morphine 0.01 gm.		
50	28	43	52
60	15	27	43
70	10	32	52
80	4	40	47
90	8	54	65
100	16	50	64
110	4	50	60
120	8	43	57
130	4	20	32
140	4	10	22
150	5	18	32

PROTOCOL VIII

Complete pouch dog

(A) Fasting

(1)

Time	Amount	Free HCl	Total
30 min.	12	110	127
60	14	106	120
	Injection of 0.5 c.c. of water		
90	16	118	128
120	13	104	118
150	10	100	112
180	15	110	126
210	10	88	100

(2)

Time	Amount	Free HCl	Total
30 min	6	45	51
60	11	80	91
90	10	88	98
120	10	84	90
150	6	80	87
180	7	78	80

(3)

Time	Amount	Free HCl	Total
30	15	90	115
60	14	100	122
90	8	80	93
120	9	82	95
150	10	80	90
180	10	78	90

(4)

Time	Amount	Free HCl	Total
30	10	37	55
60	5	32	50
90	7	45	60
120	9	16	30
150	6	20	42
180	8	31	41

(B) After feeding

(1) Slice of bread

Time	Amount	Free HCl	Total
30 min	30	110	114
60	35	130	132
90	30	120	122
120	30	105	112
150	24	121	130
180	20	100	106

(2) Milk 200 c.c.

Time	Amount	Free HCl	Total
30 min.	20	109	111
60	27	104	131
90	40	121	128
120	35	124	130
150	47	131	135

(3) Regular feeding

Time	Amount	Free HCl	Total
30 min	30	120	124
60	40	130	134
90	45	126	128
120	35	124	130
150	30	120	127

(4) Regular feeding

Time	Amount	Free HCl	Total
30 min	55	131	134
60	44	132	135
90	30	110	120
120	32	15	134
150	15	110	124

(C) After morphine injection

(1) Depressive response

Time	Amount	Free HCl	Total
30 min	22	90	97
60	17	100	105
	Morphine 0.004 gm		
90	4	60	63
120	8	40	57
150	6	35	54
180	4	10	14

(2) Transient Stimulation

Time	Amount	Free HCl	Total
30 min	10	62	84
	Morphine 0.004 gm		
60	14	88	4
90	22	60	104
120	20	104	130
150	12	70	82
180	4	6	14
210	4	6	6
240	5	6	6
270	6	6	6

(3) Effect of feeding after morphine injection

30 min	15	87	97
60	15	91	103
	Morphine 0.004 gm		
90	10	63	73
120	3	11	14
150	2	4	6
	No food		
180	15	73	87

(4) Effect of morphine during digestive period

30 min	60	104	164
210			
	Morphine 0.004 gm		
240	42	119	114
270	24	102	102
300	14	104	107
330	24	114	115

PROTOCOL IX

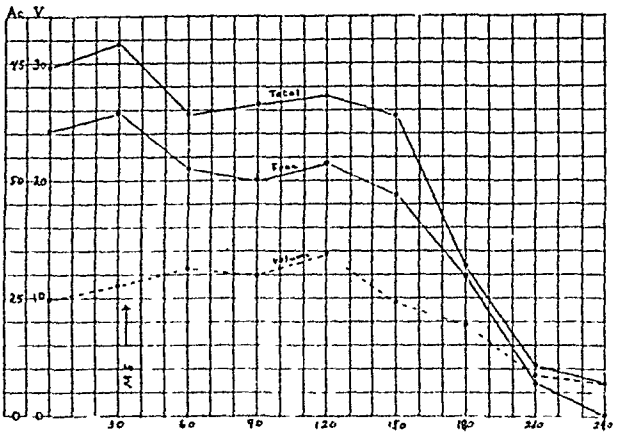
Pavlov pouch dog

(A) Fasting			
Time	Amount	Free HCl	Total
30 min.	2	0	6
60	2	0	7
90	1	0	5
120	2	0	5
150	2	0	5
180	3	0	5
210	4	0	8
240	2	0	10

(B) After feeding			
Time	Amount	Free HCl	Total
120 min.			
150	15	54	94
180	12	94	116
210	10	66	120
240	15	80	90
270	12	80	95

(C) After morphine injection			
30 min.	2	0	5
60			
Morphine 0.004 gm.			
90	3	0	10
120	7	25	43
150	17	32	48
180	6	21	35
210	6	16	35
240	2	3	16

(D) After morphine injection			
30 min.	2	0	10
60	3	0	10
Morphine 0.012 gm.			
90	14	0	12
120	10	18	31
150	20	61	69
180	18	56	70
210	3	28	36
240	3	6	26



Graph 7. A composite curve showing the effect of morphine on gastric secretion in a dog with complete stomach pouch. (Result of fifteen tests).

studied showed a reduction of volume and approximately 50% a corresponding drop in the free acidity. Only in 4 instances did a mild increase of the acidity take place after the injection of the drug. The depressive effect was found to be more marked when the patient was quiet and drowsy under the influence of morphine. The inhibitory action of morphine was, on the whole, rather weak for it was easily overcome by stimuli of chemical, psychic, or gastronomic origin. The effects of small doses of morphine in the dog were inconsistent. In one dog, morphine seemed to produce a mild stimulation, while in the other, both stimulation and inhibition were observed on different occasions. The difference in results between man and dog is probably due to the fundamental difference in their respective reactions towards the particular drug.

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E. Histolytica and Other Protozoa in the Personnel of a Chicago Hospital*

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DURING November and December of 1935, nine active cases of amebic dysentery were found among the personnel of a Chicago hospital. The medical department of the hospital examines and treats all employees who report themselves sick and unfit for duty. In the course of such examinations in the two months mentioned above, 11 persons were found to have Entameba histolytica in the feces. Nine of the 11 complained of gastro-intestinal symptoms. Specimens from the other two persons contained principally cystic forms of the parasite, and there was no diarrhea or other intestinal complaint.

These findings and the general alarm among the remainder of the personnel made necessary a thorough investigation of the extent of amebic infestation; and at the same time the plumbing was carefully checked. Food-handling procedures were also investigated and the first fecal specimens to be examined were those from the food handlers.

Although the main subject of this report is the result of the fecal examinations, a brief summary of the plumbing defects will be given here. An inspection† of the water supply and sewerage facilities of the main hospital building, annexes, and nurses' home was made November 29th and 30th, 1935. The water supply for the entire institution is obtained from the City of Chicago. Water is taken from Lake Michigan, chlorinated and delivered to all consumers without further treatment. Chicago water pressure is not sufficient to serve the upper floors of the institution directly, and booster pumps are needed to raise the pressure sufficiently for service on these upper floors. There are, therefore, two general cold water piping systems in the institution and in addition an iced drinking water system consisting of a cylindrical steel cooling and storage tank, and a small electrical booster pump.

Field analyses of water collected during the inspection showed it to be bacteriologically safe and to have a residual chlorine content of 0.2 part per million. Sanitary wastes from the entire institution are discharged into the Chicago sewer system. The institution is equipped with scores of water-flushed toilets, lavatories and sinks in addition to many other plumbing appliances, such as hydro-therapeutic baths, utility sinks where bed-pans and urinals are washed, instrument sterilizers, etc. Many places were found where possible back-siphonage of sewage might occur. All toilets in the institution are of the "flushometer" valve type where the water supply has a direct pressure connection to the toilet. In case of stoppage of the toilet, the level in the bowl could rise until the water inlet would be submerged. If this occurs at a time when the water supply is cut off for any reason, the opening of a cold water tap in the same line below the flooded toilet would cause sewage to be siphoned into the water supply. None of the toilets in the institution were equipped with siphon-breakers at the time of the inspection. All utility sinks and most of the lavatories were found to have faucet inlets located below the top rim of the sink, making it possible for these inlets to be submerged whenever the drain might become clogged. At times when these inlets are submerged, if a water shut-off occurs, back siphonage of bed-pan and urinal washings may take place. This would introduce dangerous contamination into the water supply.

It was found during the inspection that five of the six instrument sterilizers on the operating floor had direct overflow and drain connections to the sanitary sewer. If the drain line to these sterilizers were to become clogged, sewage might actually run into the instrument sterilizers. With such occurrence it might be possible for instruments used during operations to become seriously contaminated; in addition, the water supply would be subject to possible pollution.

In order to make the water supply and sewerage facilities safe and sanitary, the following recommendations were made:

1. Make a complete plumbing survey of the entire institution in order to locate every place where it would be possible for back-siphonage to occur from plumbing fixtures to the water supply system, and correct such conditions.

2. Install satisfactory siphon-breakers on all toilets equipped with "flushometer" type valves.

3. Change the water service inlets where necessary at all lavatories, sinks, slop sinks, hydro-therapeutic baths, etc., so that all inlets will be at a level high enough to preclude the possibility of their being submerged at any time.

4. Prohibit the use of hose at slop sinks or on any other equipment where such practice may permit back-siphonage to occur even though the plumbing fixtures may be properly designed and installed.

5. Provide atmospheric vents on the drain lines from all instrument sterilizers.

6. Incorporate immediately a practice at the institution that no plumber or other person shall be permitted to close a valve on a water supply main without authority of the master mechanic, who shall first notify all persons in charge of those parts of the building which will be affected by such shut-off so that no

* The Bureau of Laboratories of the Illinois Department of Public Health and the Department of Preventive Medicine and Public Health, University of Illinois College of Medicine, Chicago.

† The inspection was made by the Division of Sanitary Engineering, Illinois Department of Public Health. The sanitary features presented here are from the report submitted by this Division.

Submitted June 8, 1936.

attempt will be made to draw water from the shut off portion of the system until repairs are completed and water under pressure is again available. This practice should be continued until all plumbing fixtures have been corrected where necessary to prevent back-siphonage of sewage to the water supply system.

The foregoing recommendations were carried out exactly as outlined. In addition to the regular maintenance crew, extra plumbers were employed and the work of correcting plumbing defects was begun and carried to completion as soon as possible. Siphon-breakers, totalling 192 in number, were installed on all toilets, utility sinks, and other equipment in which submergence of the water inlets might occur as a result of clogged drains. Lavatories and other sinks were fitted with new faucets of such design that the delivery spouts were above the highest level of the bowl rims. Drains to all sterilizers and water stills were changed to open funnel types, so that any back-flow of sewage would run out on the floor and not into the apparatus.

PROTOZOA SURVEY

Arrangements were made to examine fecal specimens in one of the laboratories of the hospital. A daily schedule for the submission of specimens was laid out according to divisions of the hospital personnel. Kitchen employees were examined first, the nurses next, and later the clerical and maintenance forces, laborers, janitors, and miscellaneous groups.

Specimens were collected in paraffined paper cups and delivered to the laboratory within one hour in most cases. None of the specimens were more than two hours old in any case. Cups containing the feces were either examined immediately upon receipt, or placed in a 37° C. incubator until examined. In spite of the detailed instructions issued, a certain number of specimens contained oil. These samples were rejected by the laboratory and were not counted in our totals of examinations per person. Additional material was requested in such cases.

Direct smears in water or eosin were examined, and iodine was used for the identification of nuclear structures. In certain cases methylene blue in methyl alcohol, as described by one of us (1), was used. This stain was useful especially for trophozoites which did not exhibit a sufficiently characteristic appearance, and which failed to show nuclear structures clearly with iodine. Four to six direct smears were thoroughly searched in the negative cases. Positive smears were examined until the species identification was assured and until the examiner was satisfied that any double or multiple infestation would have been detected. All protozoa found were recorded. Specimens showing precystic forms of amebae or unidentifiable trophozoites were so recorded, and additional specimens were immediately requested.

All specimens were inoculated into the liver agar and serum medium of Cleveland and Collier (2), and were examined after 24 and 48 hours incubation. No concentration methods were attempted, nor was any use made of fixed and stained smears. Comparative stool and complement-fixation tests were planned, but not enough blood specimens were submitted to the laboratory to be of statistical significance.

Three hundred eighty-four persons were examined at least once. The greater part of these (287) were examined three or more times. All kitchen employees (68) were examined four times. Eleven hundred and two examinations were made on 384 persons, giving an average of 2.9 examinations per person.

RESULTS

The percentage distribution of amebae and flagellates is shown in Table I. The total is larger than the actual number of persons examined because of multiple infestations in 42 of the subjects.

TABLE I

Intestinal Protozoa found in personnel of a Chicago Hospital (384 persons)

Protozoa	Persons	Percent
E. histolytica	24	6.3
E. coli	102	26.5
E. nana	69	18.0
I. butschlii	9	2.3
C. mesnili	11	2.9
G. lamblia	10	2.6
T. intestinalis	1	0.3
Negative	201	52.3

Dientameba fragilis was not encountered in this group of specimens. Single species of protozoa were found in 141 persons; 41 had two species, and one person was infested with three species of protozoa. Of the 24 persons harboring E. histolytica, 13 were discovered on the first examination. Five additional ones were found during the second examination. The remaining 6 were diagnosed in the third to fifth examinations. Table II shows the above data in a cumulative form.

TABLE II

Cumulative findings of E. Histolytica by repeated fecal examinations in a group of 384 persons

Examinations	Number Found	Percentage of Total
One	13	54.2
Two	18	74.2
Three	19	79.2
Four	23	95.8
Five	24	100.0

During surveys such as this, the microscopist often suspects the presence of E. histolytica in a certain number of specimens without actually finding perfectly typical forms on which to base a diagnosis. Such suspected cases or carriers should be removed at once from food-handling duties or other situations in which they might be likely to infect other persons. Additional specimens may then be obtained and the diagnosis definitely made. Considering this survey on the above basis, 95.8% of the positives were identified *or suspected* in two examinations.

Since all specimens were cultured, a comparison can be made of the relative efficiency of cultures and direct microscopic smear examinations. In six instances the smears were positive for E. histolytica on specimens

for which the cultures were negative. In one instance the culture was positive while the smears were negative on first examination. Amebae were detected in the examination of a second specimen from this person.

The positive findings of E. histolytica were on persons widely scattered throughout the institution. No particular occupational group or single department had a disproportionately large number of positives.

DISCUSSION

The 6.3% of persons found positive for E. histolytica is within limits ordinarily given as the normal incidence for the United State. These findings are higher, however, than those Kaplan, Williamson and Geiger (3 and 4) reported for Chicago food-handlers in 1927 and 1929. Their first report on a group of 720 food-handlers showed an incidence of 2.22% positive E. histolytica. The second report on 1,148 personssons gave an incidence of 2.35%. Statistical data on the findings in the Chicago outbreak of 1933 have not as yet been published. Johnstone Davis and Reed (5) found 9.2% E. histolytica infestation in 1,000 prisoners at San Quentin in 1933. In the same report they tabulate findings of other investigators on various groups of subjects, totaling 11,565 individuals. The average histolytica incidence for this large number of persons, all of whom were examined in California, was 12%. Since the above data are for residents of California, they are not properly comparable to what might be found under different conditions in Chicago.

Our findings on the hospital personnel do not point definitely to any one source of infestation. The sanitary inspection revealed many conditions which would allow possible pollution of the water supply. With such a large number of plumbing fixtures it is inevitable that water shut-offs are frequently necessary in order to make repairs and to clear drains which have become stopped. The possibility of transmission by food-handlers is also present. Among the kitchen employees there were three persons infested with E. histolytica. Whether they received their infestation by the same means and at the same time as the others, or whether they were the source from which the others were infested, is of course unknown. In addition to the foregoing possibilities, there is also the factor of outside sources from which any of the group might have acquired the parasites.

Correction of the plumbing defects is expected to end the possibility of water transmission. To remove the likelihood of transmission by food, all cases and carriers were treated until proved negative by at least four stool examinations. All new employees are to be examined four times before approval for service in the hospital.

SUMMARY

1. Nine cases of amebic dysentery and two carriers were found among sick employees of a Chicago hospital. A survey of the remaining 384 employees revealed 24 additional carriers of E. histolytica.

2. An inspection of the water and sewerage arrangements revealed numerous faulty conditions by means of which the water supply might have become contaminated. Transmission by food-handlers was also possible, since three of the kitchen employees were infested.

3. Careful microscopic examination of fresh fecal specimens was found to be superior to the cultural methods employed in this survey.

4. Examination of two specimens per person was sufficient to reveal or place under suspicion 95% of the carriers actually found.

5. The control measures consisted of correction of all plumbing defects and treatment of all cases and carriers until free from E. histolytica, as shown by repeated negative stool specimens. New employees must be free from infestation before being accepted.

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The Colon in Mental Disease*

I. Dementia Praecox

By

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ALTHOUGH much has been written about the emotions and the effect produced by them upon the gastro-intestinal tract, a comparatively few objective studies have been carried out upon man, and even fewer upon him when his emotions are most abnormal, i.e., when he is psychotic. It is certainly reasonable to expect to find in the psychotic individual the most pronounced and prolonged of emotional states; this being unquestionably true, and if emotions alter the functioning of the gastro-intestinal tract, then the most profound and prolonged of functional alterations should be observed in the gastro-intestinal tracts of psychotic individuals.

It is the purpose of this paper to present a study of one portion of the gastro-intestinal tract, the colon, in one type of mental disease, dementia praecox.

*From the [illegible] Boston State Hospital.
[illegible] June 2, 1934

TABLE I

Showing relationship between emptying time and colon tonus, body types and mental state

	Emptying Time of Colon in Hours						
	Normal 48 hours	96 hours	144 hours	192 hours	240 hours	288 hours	336 hours
1. Total Cases	14	14	9	3	3	3	2
2. Colon Tonus							
a. Decreased	4	4	2	1	1	2	2
b. Normal	2	4	3	1	1	1	0
c. Increased	8	6	4	1	1	0	0
3. Body Type							
a. Pyknic	2	8	2	1	1	0	0
b. Athletic	0	4	2	0	0	0	0
c. Asthenic	12	2	5	2	2	3	2
4. Mental State							
a. Indifferent	10	11	6	2	2	2	2
b. Agitated	2	1	0	1	1	1	0
c. Tense	2	2	3	0	0	0	0

METHOD

The individuals used for this study were all definitely mentally ill and sufficiently so to be admitted to the hospital for an indefinite period of treatment. The psychosis, dementia praecox, was considered as a clinical entity with the principle features limited to (a) primary progressive deterioration, (b) autistic or deristic withdrawal from the environment, and or (c) intellectual incoordination. The psychosis in each individual was considered to be chronic. All of the patients were men, women being excluded from this initial work because of the possible complicating factors of catamenia.

Each patient was given two cleansing enemas, one following the other, about two hours before the examination and shortly after the noon-day meal. No attempt was made to interfere with the regularity or quantity of food eaten. At the prescribed time the patient was given a barium enema, the barium mixture being run in under gravity until the colon was apparently filled. The maximum quantity of barium mixture given to any one patient was 2,000 c.c. The filling was determined by leaving the rectal tube in place until no more barium would flow into the colon. The entire procedure was followed under the fluoroscope.

The patient was permitted to evacuate then as much of the enema as he wished, and his colon again observed under the fluoroscope. The rate of emptying and the tonus of the colon were studied every other day under the fluoroscope until the colon had emptied itself of barium. Throughout the procedure the patient was permitted to resume his regular dietary habits and physical activities. The maximum normal emptying time of the colon was considered to be 48 hours. The emptying time and the tonus were correlated with each other and with the body type and mental state of the individual.

RESULTS

In the 48 cases of dementia praecox studied, the ages ranged, at the time of the study, from seventeen to forty years. Some of the patients had been mentally ill for as long as ten years. No individual had been ill less than one year. In no instance could anything abnormal be found in the size, shape, position or contour of the colon. The musculature of the abdominal wall was good in forty-four and poor (lax) in four of the cases. In the four cases with poor abdominal tone no relationship could be established between the poor tone and the colon emptying time and tonus. The dominant emotional states, subjective and objective, of the patients were classified as, indifferent 35, agitated 6, and tense 7. The tonus of the colon was decreased in sixteen cases, normal in twelve cases and increased in twenty cases. The emptying time of the colon was 48 hours for 14 cases, 96 hours for 14 cases, 144 hours for 9 cases, 192 hours for 3 cases, 240 hours for 3 cases, 288 hours for 3 cases, and 336 hours for 2 cases.

The relation between the emptying time and tonus of the colon and between each of these and the body type and mental state of the individual is shown in Tables I and II.

TABLE II

Showing relationship between colon tonus and body type and mental state

	COLON TONUS		
	Decreased	Normal	Increased
1. Body Type			
a. Pyknic	2	4	8
b. Athletic	0	2	4
c. Asthenic	14	6	8
2. Mental State			
a. Indifferent	14	9	12
b. Agitated	0	1	5
c. Tense	2	2	3

From a study of the material presented in these tables the following facts are evident:

1. The tonus of the colon was normal in 25 per cent of the cases and abnormal in 75 per cent of them. Of the cases in which the tonus was abnormal, in 44

per cent it was decreased and in 56 per cent it was increased.

2. The emptying time of the colon was normal in 29 per cent of the cases and abnormal in 71 per cent. In those cases in which it was abnormal 41 per cent emptied in 96 hours, 26 per cent in 144 hours, 9 per cent in each of 192, 240 and 288 hours and 6 per cent in 336 hours.

3. Where the colon tonus was normal only 16.6 per cent of the cases emptied within the normal period, whereas 33 per cent emptied in 96 hours, 25 per cent in 144 hours, and 8 per cent in each of 192, 240 and 288 hours. Where the tonus was decreased 25 per cent of the cases emptied within the normal period, 25 per cent in 96 hours, 12.5 per cent in 144 hours, 6 per cent in each of 192 and 240 hours, and 12.5 per cent in each of 288 and 336 hours. Where the colon tonus was increased 40 per cent of the cases emptied within the normal time, 30 per cent in 96 hours, 20 per cent in 144 hours, and 5 per cent in each of 192 and 240 hours.

4. When the relationship existing between the emptying time of the colon and the body type of the individual was investigated it was found that where there was a pyknic body habitus the colon emptied normally in 14 per cent of the cases, in 96 hours in 57 per cent, in 144 hours in 14 per cent, and in each of 192 and 240 hours in 7 per cent of the cases. Where the body habitus was athletic the colon emptied normally in no instance, but 66.6 per cent of the cases emptied in 96 hours, and 33.3 per cent in 144 hours. Where the body type was asthenic 42 per cent of the cases had colons which emptied normally, 7 per cent emptied in 96 hours, 18 per cent in 144 hours, 7 per cent in each of 192 and 240 hours, 10.7 per cent in 288 hours and 7 per cent in 336 hours.

5. When the relationship existing between the tonus of the colon and the body type of the individual was investigated it was found that in those cases with pyknic body habitus 28.5 per cent had a normal colon tonus, in 14 per cent of the cases it was decreased and in 57 per cent it was increased. In the cases with athletic body habitus 33 per cent had a normal colon tonus and 66.6 per cent had an increased colon tonus. In those cases with asthenic body habitus 21 per cent had a normal colon tonus, 50 per cent had decreased tonus and 28.5 per cent had increased tonus.

6. When the dominant emotional state was investigated relative to its relationship to the emptying time of the colon it was found that of the cases whose emotional state was characterized by indifference 28.5 per cent had colons emptying normally, 31 per cent emptying in 96 hours, 17 per cent in 144 hours and 5.7 per cent emptying in each of 192, 240, 288 and 336 hours. Where the dominant emotional state was agitation 33 per cent of the cases had colons which emptied normally and 16.6 per cent emptied in each of 96, 192, 240 and 288 hours. Where the dominant emotional state was characterized by tenseness 28.5 per cent of the cases had colons which emptied normally, 28.5 per cent in 96 hours and 42.6 per cent in 144 hours.

7. When the dominant emotional state was investigated relative to its relationship to the colon tonus in those cases whose emotional state was characterized by indifference 25 per cent had normal colon tonus, 40 per cent had decreased tonus and 34 per cent had increased colon tonus. In those cases whose emotional state was one of tenseness 28 per cent had normal colon tonus, 28 per cent had decreased tonus and 43 per cent had increased colon tonus. In those cases whose emotional state was one of agitation 16.6 per cent had normal colon tonus, and 83 per cent had increased tonus.

DISCUSSION

In 1930 Alkan (1) wrote that the psychic processes influence the small intestine and colon in various ways; that according to our knowledge they alter secretion comparatively rarely, but the motor functions all the more frequently. The small intestine, he feels, is the end-organ of psychic alterations, but that these alterations manifest themselves much more frequently in the colon, in a spastic as well as in an atonic manner; that every kind of psychic excitation may show itself in constipation, which is, for the most part, spastic.

Alkan quotes Fleiner as saying: "Diagnostically these X-ray pictures of the colon are often of more value than the patient's facial expression, which can be controlled voluntarily or distorted conventionally, the result being an expression which is harmless and well balanced. The expressive movements of the colon as they appear in the picture, on the other hand, do not deceive, they are unfalsifiable and unmistakable. Questioning many patients as to their attitudes and experiences and moods, only after having looked at their intestinal pictures, I then obtained unrestricted information."

Substantiating these observations are those of Adolf Meyer (2) who in a paper which he read before the American Gastro-enterological Association in 1932 stated, "Instead of leaving the impression that in most cases we have to probe at once into the sex life when we suspect 'mental factors' to be playing a role, I should emphasize the fact that after all practically every fundamental function can take a lead in the personality constitution, in this sense, that, for instance, the gastro-intestinal function may have just as much of a tendency to express the personality as the sex function and *to be* 'the personality' in certain situations and in certain periods of life. I should say that the gastro-intestinal receptive, digestive and eliminative functions can become that which expresses, and leads to the government of, the person for certain periods of the day or throughout life as a dominant and leading concern."

This personality, states C. Macfie Campbell (3), if adequately conceived, represents the total system of forces, including both those conscious and expressed and those subconscious and repressed. Furthermore, he continues, the personality and the psychosis are not independent concepts: the psychosis is the personality; it is the individual in action; one phase of an individual existence.

This personality consists, then, of the sum total of chemical, physiological, emotional, overt and intellectual spheres of an individual which under average conditions in a normal person have a socially satisfactory balance. When an individual becomes psychotic, *i.e.*, when his personality deviates from the socially accepted standards of conduct there is some abnormality in the balance of the chemical, physiological, emotional, overt and intellectual spheres. In dementia praecox there is usually a definite abnormality in the emotional, overt and intellectual spheres, and this was found to be particularly true of the cases used in this study. Since there are marked personality deviations in dementia praecox, and since the gastro-intestinal tract

may have a tendency to express the existing personality, this study of the colon should reveal some facts relative to the physiological aspects of dementia praecox.

A survey of the results presented in this paper would tend to indicate:

(a) There is a certain number of individuals in a dementia praecox group in which there is an abnormality in the emptying time and/or tonus of the colon.

Thus in 75 per cent of the cases the tonus was abnormal of which group it was decreased in 44 per cent and increased in 56 per cent. Furthermore in 71 per cent of the cases of the entire group the emptying time was abnormal; *i.e.*, delayed. The tonus and emptying time of the colon were both decreased in 25 per cent of the group. The tonus was increased and the emptying time decreased in 25 per cent of the group. Therefore in dementia praecox, although it is highly probable that the tonus or the emptying time of the colon will be abnormal (3 chances in 4), the probability of the tonus and emptying time being abnormal is less (1 chance in 2) and the probability of the tonus and emptying time both being decreased still less (1 chance in 4). On the other hand the chances of the tonus and emptying time of the colon both being normal are 1 in 24. It is thus perfectly obvious that although it is possible that the tonus *or* emptying time of the colon may be normal (tonus or emptying time either have about 1 chance in 4 of being normal) the chances of both being normal in the same individual are rather remote (1 chance in 24). This being so one would be justified in concluding that in dementia praecox in the majority of cases there would be found an abnormality in the emptying time and/or tonus of the colon.

(b) Inasmuch as there was no clinically discernable pathology capable of producing the observed colon abnormality, the existing psychosis, dementia praecox, must be a contributing factor, at least, in this abnormality.

The patients used in this study were felt to be clinically normal. They all ate well and lived a fairly regular institutional life. All were adequately nourished. Such factors as under or over-nourishment could definitely be eliminated. The amount of physical exercise was uniform throughout the group inasmuch as none were under nor overworked. Their routine life was not unlike that of the average man on the outside. The type of food was standardized and although any individual could have all he wished, it was controlled in that he must eat a maintenance diet and a balanced one. The musculature of the abdominal wall in the group was good in 44 cases and lax (poor) in 4 cases. It is relatively certain that none of these factors could have played a very important part in producing abnormalities in the tonus and emptying time of the colon. The body type was then studied in its relation to the colon tonus and emptying time in order to determine its effect. There were 14 cases with pyknic body habitus, 6 with athletic body habitus and 28 with asthenic body habitus. Of those with pyknic habitus 12 had abnormal colon emptying time and 10 abnormal colon tonus (in 2 cases it was decreased and in 8 increased). Of those with athletic habitus 6 had abnormal colon emptying time and 4 had abnormal colon tonus (in all 4 cases it was increased). Of those with asthenic habitus 16 had abnormal colon emptying time and 22 abnormal colon tonus (in 14 cases it was decreased and in 8 increased). It is clear that there is possibly some correlation between decreased emptying time of the colon and body habitus; *i.e.*, that the pyknic and athletic body types were encountered in far greater numbers where decreased colon emptying time was found than the asthenic body type. It is also clear that there is very little correlation between body habitus and colon tonus as a whole or between body habitus and increased colon tonus, but that where the tonus is decreased there will be more individuals with the asthenic habitus than with the pyknic and more in the pyknic habitus than with the athletic. Thus, whereas the colon tonus was decreased most frequently in association with the asthenic body habitus it was in this same habitus that the colon emptying time was least frequently found decreased. Work at the present is being continued to determine the accuracy of these findings in other psychotic groups. If the work which has been done by others on the relationship between the body habitus and psychosis may be accepted, the observations on the relationship existing between the body habitus *and* colon tonus and emptying time can easily be explained on the basis of the relationship existing between the psychosis and the body type, with the latter as a common finding. This has been pointed out by Henry (4) who attempted to show that the amount that the gastro-intestinal tonus and motility were effected by body habitus was relatively unimportant as compared with the variations accompanying schizophrenia.

(c) Dementia praecox, as it is conceived today, is a mental illness characterized by supposed marked deviations from the normal in personality, which deviations are emotional, overt, and intellectual. The changes in body chemistry or physiology found in an individual with dementia praecox are an expression of his psychosis and may not only reflect it but contribute to it.

A normal individual is usually considered as an entity in existence; as an individual reacting to his internal and external environment and expressing this reaction by thought, word or action. Upon occasion some emotional tension will bring about some physiological response which we are able to observe; such as, shaking in fear, crying in sorrow, striking in anger. These physiological responses are all the result of the emotion, certainly not the cause of it. Such responses can also be participated in by the gastro-intestinal tract, as when a reaction to an emotion occurs such as nausea and vomiting in disgust, constipation when worried, and sudden evacuation in moments of intense fear and excitement. These reactions are all logical and have repeatedly been explained by the equation—strong emotion reacts upon the autonomic nervous system which in turn elicits certain specified responses from the periphery. If this equation can be applied to a normal physiological response to a normal emotion there is no reason why it should not be applied to psychotic individuals thus: strong emotion with or without normal basis reacts upon an autonomic nervous system producing a physiological response which to the observer may appear incongruous but which, when all the facts about the train of events are known, is not incongruous but entirely logical and rational. If this is accepted as a reasonable working basis then it is entirely possible that the abnormalities of colon tonus and emptying time may have some rational, if not evident, basis. Thus the response of the colon to the emotion is an expression of

the psychosis and if the response assumes malignant proportions (such as retention of feces for days until such retention may produce physical symptoms) then the physiological response may contribute to the symptomatology of the psychosis.

(d) The colon tends to demonstrate that the personality of dementia praecox is not a uniform state but varies within the group as does the personality of any group of individuals. Thus the group designated as dementia praecox is not uniform but rather heterogenous.

If only the colon in dementia praecox is taken as an index or expression of the personality, or even as *the personality* as Dr. Adolf Meyer has considered it, it is at once obvious that the "colon personalities" of dementia praecox are not uniform. There is the colon that has a normal emptying time and then there are the colons with all degrees of delayed (indifferent) emptying times. Or there is the colon with decreased tonus, normal tonus, and increased tonus. Or if these two are considered as aspects of the "colon personality" then there are personalities which the colon expresses by decreased tonus, normal emptying time; decreased tonus, decreased emptying time; normal tonus, normal emptying time; normal tonus, decreased emptying time; increased tonus, normal emptying time; and increased tonus, decreased emptying time. This may appear to be an odd manner in which to describe a personality but is no more odd than to describe a personality in terms denoting inferiority, shyness, embarrassment, clumsiness, etc., all of which denote some physical or chemical state which is reflected by some more complex physiology. Again, if the personality may be described thusly and since all of these personality types were found in varying degrees and quantities in the studied dementia praecox group, the assumption is justified that either there are all types of personalities in a dementia praecox group or that the group of psychotic individuals called dementia praecox is a heterogenous one.

(e) The observed and objectively dominant emotions as expressed by the patient are not in every or many instances reflected by the colon. If the colon does express or reflect the personality of the individual then the observed and objectively dominant emotions of dementia praecox are misleading and probably a blind to the true personality.

In the group of individuals in this study their dominant emotional state was described as indifferent 35 cases, agitated 6 cases and tense, 7 cases. Where indifference was dominant 25.6 per cent of the cases had a normal colon tonus and 74.4 per cent an abnormal tonus (40 per cent decreased and 34.2 per cent increased); and in 28.5 per cent the emptying time was normal and in 71.5 per cent it was decreased. Where agitation was dominant the tonus was normal in 16.6 per cent of the cases and abnormal in 83.0 per cent (83.0 per cent increased); and in 33.3 per cent the emptying time was normal and in 66.6 per cent abnormal. Where tenseness was dominant the tonus was normal in 28.4 per cent of the cases and abnormal in 71.6 per cent (28.4 per cent decreased and 42.6 per cent increased); and in 28.5 per cent of the cases the colon emptying time was normal and in 71.5 per cent abnormal.

The correlation between the observed dominant emotional state and the tonus and emptying time of the colon was obviously very low. This was rather startling when one took into consideration the prevailing researches into this field. But possibly it can be explained. This low correlation may be due to (1) the actual existence of no relationship between emotions and gastro-intestinal response and vice versa; (2) the observed dominant emotional state not reflecting the true personality; or (3) the colon not reflecting the true personality.

The work of Cannon, Pavlov and a host of others would tend to indicate that there is a definite correlation between emotions and the gastro-intestinal physiology, and, moreover that the gastro-intestinal tract can to a certain extent be conditioned by the emotions. This would nullify (1).

In dementia praecox the objective psychotic state is frequently a mask or shell behind which, and thoroughly concealed, resides the true personality of the individual. It is unusual for a person with dementia praecox to exhibit his real personality, his real reactions to his total environment being something which he has withdrawn from reality and which belongs to him. This has been clinically demonstrated by many workers in this field and would tend to substantiate (2).

It is rather hard to conceive of the gastro-intestinal tract acting in a voluntary manner—of it taking the initiative with no stimulus whatsoever and setting the pace whereby false observations are liable to be made. It would appear that since the chemistry and physics of the gastro-intestinal tract are controlled by the autonomic nervous system that any functioning of the tract would be in response to some stimulus which would be controlled by this system. Since this system is not conscious, it is only reasonable to assume that it could not voluntarily be controlled; that the functions of this tract would be true reflections of stimuli whether they be emotional (conscious or unconscious), chemical or physical, overt or intellectual. If this all be true, and it is, then (3) is eliminated.

Thus, we find that (a) emotions do affect the gastro-intestinal tract and can condition it (b) these emotions can be conscious or unconscious (c) they can be completely concealed by superficial or false emotions which act as a blind giving the real emotions room for free play (d) the colon which is not subject to such concealment reflects the true emotional state of the individual.

(f) In the majority of cases of dementia praecox there is some imbalance of the autonomic nervous system as expressed by studies of the colon.

There is no question but that in the study presented herein, in the colons of individuals with dementia praecox there is a definite abnormality in the emptying time and/or tonus in a large number of cases. As is well known the normal functioning of the large bowel is dependent upon a normal balance existing between the sympathetic and parasympathetic nervous systems. When there is some imbalance, regardless of the precipitating factor or factors, there results

abnormal functioning of the colon. Since in many cases of dementia praecox there exists this abnormal functioning of the large bowel, it would appear unnecessary to ascribe it to any other mechanism than to the autonomic nervous system imbalance. The mechanism underlying this imbalance is in most all probability the emotional, overt and intellectual imbalance which constitutes the psychosis.

SUMMARY

A study of the emptying time and tonus of the colon in dementia praecox is presented.

It was demonstrated that in the majority of instances there was an abnormality in the functioning of the colon.

The possible mechanisms underlying this abnormality are discussed in detail.

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Gastroscopy

Observation in 100 Cases*

By

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THE introduction of gastroscopy into the field of diagnosis and research, marks one of the truly great advances in the realm of gastro-enterology. We have included the gastroscope as one of the important means at our disposal in this direction, and have during its employment, made certain observations which may be of interest not only to the clinician but the endoscopist as well.

To begin with, the choice of the patient for gastroscopy is not limited or confined to a certain type of individual or group of diseases to be considered. Mindful of the contraindications to the procedure which must at all times be respected, patients with symptoms referable to the gastro-intestinal tract are explored by means of this method after a detailed physical, chemical and roentgenologic examination has been undertaken. That the procedure of actual gastric inspection fills a definite need in the evaluation of problems dealing with alimentary affections, and offers promise of still further benefits as our perception and knowledge develop, can be surmised on the basis of past experiences and contributions in this difficult field.

Up to most recent times, the oft repeated references to technical difficulties and dangers to the patient, arising out of a gastroscopic examination was emphasized and served to retard rapid progress in the development of knowledge. The Wolf-Schindler apparatus, as previously suggested, has to a considerable degree solved many past objections, although the technique of gastroscopy has to be learned and practiced, often with perseverance and after disappointments. In short, there is no royal road to the desired goal, nor is this reflection intended to be construed as suggesting such colossal technical difficulties as may not be surmounted by the serious application of the prospective enthusiast.

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Submitted December 15, 1935.

METHOD OF EXAMINATION

We begin the examination of the patient in the manner outlined by Schindler. It is insisted upon, that neither food nor drink be allowed for at least 12 hours prior to the examination. A reduction to a 6 hour interval between the intake of food and the instrumentation, resulted in the occurrence of a markedly congested mucous membrane of the entire stomach, so that it is advisable to maintain the longer fasting period, and thus minimize errors in interpretation. In one patient, with a marked gastric retention consequent on an organic obstruction at the pylorus, it was found necessary to lavage the stomach on the evening prior to the examination until the washings were completely clear. To this end, several gallons were required, yet despite every precaution towards obtaining the most favorable factors for visualization, the inspection of the gastric cavity was conducted under more than the usual difficulties as a result of the increased quantity of secretion inside of the organ. It is preferable not to lavage the stomach in any circumstances immediately prior to instrumentation so as to avoid marring the visual field.

In the matter of anaesthesia and general attitude and behavior of the patient, it is important to recognize, that time and patience are requisites for a proper technique. After the preliminary hypodermic injection of codeine gr. ½ and atropine sulphate gr. 1/100 fully ½ hour is allowed before the topical application of the anaesthetic to the throat is applied. This latter procedure likewise consumes another half hour. Hurrying at this stage does anything but help simplify the introduction of the gastroscope, and in a few instances where it was attempted, greater effort was required on the part of both the subject as well as the examiner.

Incidently, one cannot determine at the onset just how cooperative the patient is going to be, and how simple or difficult the procedure. The mere fact that the patient is scheduled for a gastroscopy is no assurance that a satisfactory gastric exploration will at all times be accomplished. Naturally, this factor is to be appraised in some degree in the light of the skill of the endocopist, but the fact must be recognized, that it is not possible to gastroscope every patient, and occasionally, even in the absence of the usually recognized contraindications of its employment, it may be considered inadvisable to proceed where undue nervousness, anxiety or lack of cooperation on the part of the patient are manifest. Nervousness, *per se*, is no contraindication to gastroscopy, but lack of cooperation is a definite drawback. We rely upon a detailed exposition of the procedure as we go along, and thus gain the confidence of the subject. This aptly called 'sermon' and its emphasis has been forcefully called to our attention by Jackson, and its observance is of paramount importance for a proper conduct of this procedure. A well trained assistant is absolutely indispensable. Only with the proper guidance of the head, can one be assured of a smooth performance at introduction of the instrument and proper visualization.

Not infrequently, we have found considerable resistance to the easy passage of the tube through the pharynx, as a result of marked tenseness or spasm of the crico-pharyngeal muscle, despite every exhortation towards relaxation or swallowing. However, it was seldom found necessary to give up the procedure except where fear or lack of cooperation permitted no other choice. In this connection, it might be well to remind one of the necessity for guiding the tube so that it does not get caught in the left pyriform sinus. It does not ever appear to find its way into the right pyriform sinus. We have not found any occasion where the larynx was entered although this is a possibility. It is important to remember that enforced pressure at any time during the procedure is dangerous, not only to the patient but to the instrument as well. At the present stage, the optical system of the gastroscope can readily be dislocated, resulting in damage to the lens system, but we have been up to the present, fortunate in this respect. It is at the 'diaphragmatic pinchcock' where occasional difficulties have been encountered. A spasm of the lower esophagus, occasioned by the presence of the tube has been met with, and has the effect of obstructing progress into the stomach, despite the administration of atropine and codeine prior to the examination. A speedy technique eliminates the frequency of such a phenomenon. Nevertheless, when present, it was found necessary to withdraw the instrument. By waiting for a few minutes, the resistance at the tip of the tube did not seem to give way, and blind forcing was deemed inadvisable. Visualization of the lower esophagus has been possible in some cases with the use of the retrograde gastroscopic tip. In three instances, the esophageal lumen was plainly illuminated up to the 20 cm. mark.

Once the technique of gastroscopy is acquired, the problem of orientation and recognition of the various mucosal changes and lesions of the gastric cavity has to be studied. It happens occasionally, that with the instrument *in situ*, the field is not illuminated. Here considerable patience and practice are required to establish a visual field, more particularly, one that includes the pylorus. The introduction of small quantities of air is required at this point, or else the instrument must be withdrawn somewhat, until the darkness disappears. Either of these procedures requires great care. A large quantity of air will tend to force the pylorus upwards out of line of the visual field and thus escape detection, or else in the attempt at withdrawal of the gastroscope, one fails in his visualization of the pylorus. The proper introduction of air can be learned only with experience. We have not encountered any ill-effects subsequent to the forceful injection of air into the gastric cavity, although such would not be advised where an ulcer of the stomach is suspected. Increased amounts of air have the tendency to flatten out the rugae, and every now and then the excess amounts are expelled by the patient during the examination. I have heard of one instance where perforation of the stomach, with air in the peritoneal cavity was noted and ascribed to the excessive introduction of air in a recent gastroscopy performed by one of my colleagues.

Of the one hundred case reports studied, the examinations in six of these were unsuccessful, partly because of the lack of cooperation on the part of the subject, and in two instances because of a generally unsatisfactory vision of the interior of the stomach subsequent to the successful introduction of the gastroscope.

COMMENT

The cases considered, offer interesting as well as instructive information with respect to certain phases and concepts of gastric disease or local expressions of general disease, in a manner which casts light on some of the darker and yet unexplained phenomena encountered in practice. A detailed analysis of the more salient observations is not contemplated within the limits of this paper. It is observed, generally, that the quantity of gastric juice as measured by the test breakfast, bears no relationship to the occurrence of inflammatory manifestations of the gastric mucosa. In all of our recordings, the routine use of the Ehrmann alcohol meal was employed in determining the degree of gastric acidity. We have been able to observe, that the mere presence or absence of acid in the gastric juice, does not of itself predicate the existence of inflammation, and by the same token, it was possible to demonstrate a definite gastric affection of the stomach wherein a perfectly normal chemical response to the stimulation of the test breakfast took place.

The association of a normal gastric mucosa in a patient suffering with duodenal ulcer has been noted by us in three cases in this series, and these findings, noted in the face of declarations of a 100% incidence of gastritis occurring in patients suffering with duodenal ulcer as noted by Konjetzny, Schminke, Orator, Puhl, etc., suggests the probability of considerable future controversy with respect to its meaning and significiance. Just what factors are responsible for this disparity in observation, which incidently, has been likewise confirmed by Schindler, still remains a problem. Are there such wide fluctuations in gastric healing as to explain these differences? It might be emphasized, that Konjetzny's observations were based on resection preparations mainly and therefore represented the end result of the medical phase of the life history of the ulcer, rather than the expression of intermediary forms and degrees of severity of patholo-

gical processes encountered during the course of an ailment.

With regard to the behavior of the stomach in diseases of the gall bladder, it has been demonstrated that variations in the degree of gastric acidity is not an unusual occurrence, (Ewald, Boas, Ohly, Duttmann, etc., and that subsequent to cholecystectomy, no alteration in this factor is brought about. (Ohly, Behm, Cohn, Rost, Popper, etc.). By endoscopic means, it has been possible to note marked gastric changes in diseases affecting the biliary passages, as well as perfectly normal stomachs. (Hohlweg, Korbsch, Gutzeit, Henning). Our experiences confirm these observations.

The not unusual occurrence of low or absent gastric acid values has been found to exist, not exceptionally, in the face of absolutely negative gastroscopic findings. In disturbances of the glands of internal secretion it has been shown that there may occur low gastric secretory levels. (R. Schmidt, H. Zondek, etc.). In Graves' disease it is not unusual to encounter an achylia gastrica. However, in a patient in my series, there was an absence of any affection of the inner lining of the stomach, which speaks for a sympathetic origin for the depressed secretion in the patient under discussion.

H. Quincke recorded the association of a complete gastric atrophy in pernicious anemia. This was subsequently confirmed by the work of Nothnagel, Lubarsch, Koch, Wallgren, Faber and others. In a series of 150 cases of pernicious anemia, Morawitz reported the presence of a total achylia in every one of them. However, occasional recognition of hydrochloric acid in this form of anemia was recorded by Naegeli, Cabot, Levine, and Ladd, Lenhartz, Strauss and others. In one instance I found no generalized atrophy, but areas of intervening healthy mucosa could be detected, in contrast to a different case, where complete gastric atrophy existed.

CONCLUSIONS

That the diagnosis of gastritis belongs entirely within the province of the gastroscope, is at the present time, generally accepted. (Gutzeit, Korbsch, Henning, Schindler, etc.). Notwithstanding the fact that clinical observation, the execution of a carefully conducted physical, chemical bacteriological and X-ray examination are absolute essentials for a proper concept and evaluation of a given case, one cannot gainsay but that gastroscopy's applicability extends into that realm where the diagnosis may be obscure and where further knowledge and investigation is endeavored.

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Mesenteric Vascular Occlusion: Report of an Instance with Acute Venous Thrombosis Following Splenic Artery Embolism and Infarction*

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FEW disease entities in medicine make their appearance so dramatically, present so obscure a picture, and run so rapidly a fatal course in a large percentage of instances, as do the cases of mesenteric, vascular occlusion.

The term "mesenteric vascular occlusion" is to be preferred to "thrombosis" or "embolism," as it includes both of these conditions, and, therefore, it is less confusing unless one refers specifically to either a thrombosis or an embolism.

HISTORICAL DATA

The first case was reported by Tiedeman in 1843. Virchow, in 1847, was the first who described the pathology. In 1863, Kussmaul and Gerhardt made the first attempt to establish a definite clinical syndrome. From then until 1904 there is a paucity of literature concerning mesenteric occlusion, at which time Jackson, Porter and Quimby collected and carefully analyzed 214 cases from the literature and their own personal experience. In 1913, Trotter published his Cambridge monograph on "Embolism and Thrombosis of the Mesenteric Vessels" in which he summarized all the work done on the subject to that date. Since then the literature has become replete with summaries and case reports, perhaps the most comprehensive of which is that of Warren and Eberhard.

It is the purpose of the present contribution to review a few of the more salient features of venous and arterial mesenteric occlusion, and to report an instance of mesenteric, venous occlusion due to a comparatively rare combination of etiologic factors.

PATHOGENESIS

The pathologic changes produced by an occlusion of either the *arterial* or the *venous* mesenteric circulation are quite constant. The end result comprises a hemorrhagic infarction of the affected bowel. When the artery is occluded by either a thrombus or an embolus, the first change noted is a distinct edema associated with a leukocytic infiltration composed chiefly of mononuclear and polymorphonuclear leukocytes. As a result, the tissues become markedly swollen. Discrete capillary hemorrhages appear and the capillaries and venules distend with blood. Villi degenerate. Necrosis and gangrene constitute the terminal pathology.

The end result of *venous* mesenteric occlusion is essentially the same, only it is brought about in a different fashion. When the collateral venous circulation is not sufficient to cope with the occlusion, the blood remains in the venous capillaries. New blood is constantly being fed to these structures by the arteries, so that eventually the veins distend and become paralyzed. This leads to an extravasation of serum and blood between the intestinal coats and the production of a hemorrhagic infarct, accompanied by gangrene.

ANATOMICAL CONSIDERATIONS

The *superior mesenteric* artery arises from the anterior surface of the aorta about 1.25 cm. below the celiac artery; it supplies the entire small intestine from the duodenal-jejunal flexure to the ileo-cecal valve, cecum, ascending colon, and one-half of the transverse colon. It has numerous branches, each of which anastomoses with the other to form 3 or 4 tiers of "arcades." Where the most distal of these twigs enters the intestine a final anastomosis takes place. Likewise, the *inferior mesenteric* artery, which supplies the remainder of the large bowel to the pelvic colon, has many anastomoses. In addition, the *inferior phrenic artery* is linked with the upper jejunal, to the hepatic, gastro-duodenal, superior and inferior pancreatico-duodenal vessels. The *internal iliac* and inferior mesenteric arteries are linked through the internal pudic, inferior and middle hemorrhoidal arteries.

The *mesenteric venous circulation* has an even more pronounced and abundant collateral circulation. The chief vessels and their branches, which correspond to the arteries, practically have similar anastomoses. In addition, there exist numerous anastomoses between the portal and systemic circulation by means of small systems of tributary veins too numerous to detail.

EXPERIMENTAL CONSIDERATIONS

Since such a rich network of arterial and venous anastomoses is present, one naturally wonders why an occlusion should produce infarction in such a great number of instances. Numerous investigators have attempted to solve this problem. Among the outstanding of these workers are Conheim, Litten, Cohn, Bolognesi, and Reich. Their results do not agree in their entirety, but they do so on certain essential points.

If the *superior mesenteric artery* is ligated at its trunk, the affected portion of the intestine is immediately thrown into violent paroxysms or spasm, lasting 2 to 3 hours; such automatically increase the peripheral resistance, and prevent a dilatation of the capillaries, upon which the establishment of a collateral circulation is entirely dependent; an infarct follows. Very few cases do not react in the above fashion, and the collateral circulation may handle the situation, but

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Fig. 1. Gross appearance of embolus in the splenic artery: infarction of the spleen, venous thrombosis, and hemorrhagic infarction of the intestines.

even that breaks down later in the patient's life when the original and primary etiologic factors are aggravated. A third possibility is that mesenteric occlusion may interfere with the circulation of the intestine only to the extent of destroying its function, but not doing so sufficiently to cause gangrene; in this fashion, a "functional" obstruction is produced.

If the occlusion is in a branch of the inferior mesenteric artery, whether or not an infarction will follow, is dependent entirely upon the size of the vessel and the amount of bowel which it nourishes.

In animals, ligation of the *superior mesenteric vein* is always associated with hemorrhagic infarction. However, in man, mesenteric venous occlusion definitely is a slower process. A great portion of the mesenteric venous circulation may be occluded before infarction results. Reich, after a careful analysis, concludes that infarction ensues only when the thrombus in the mesenteric vein extends so far into the smaller tributaries that it has reached the intestinal wall. In this manner, the clot extends into the mural "arcades," and, in so doing, prevents them from anastomosing with arcades of the adjacent free vessels, thence from emptying into the main veins above or below the superior level of the thrombosis.

INCIDENCE

The frequency with which the arterial system is involved as compared with the venous system varies according to the experiments of different investigators; both extremes are encountered. Most writers agree, however, that the incidence of arterial occlusion is greater than that of venous, in the ratio of 3:2.

The superior mesenteric artery is involved approximately 40 times more often than the inferior mesenteric artery. Three reasons have been advanced in an attempt to explain this preponderance: (1) the superior mesenteric artery has a diameter 3 times as great as that of the inferior mesenteric artery; (2) the superior mesenteric artery lies almost parallel with the aorta, whereas, the inferior mesenteric artery leaves the aorta at an angle of 45°; (3) because of its origin, the superior mesenteric artery has the first opportunity to intercept an embolus.

Primary occlusion of the superior mesenteric vein *alone* comparatively is an uncommon lesion, although there have been a few isolated instances recorded. Usually, the vein is involved terminally in a process descending from the portal vein or one of its tributaries. Thrombosis of the inferior mesenteric vein, *per se*, is of rare occurrence, and when present only occasionally results in infarction because of the elaborate collateral circulation for the relatively small area drained.

ETIOLOGY

The etiologic factors concerned in mesenteric occlusion vary. Infarction, as a result of closure of the arteries, may be due either to a thrombosis or to an embolus. Factors which predispose to thrombosis are arteriosclerosis and arteritis. Those which predispose to embolism are: (1) endocarditis, (2) cardiac parietal thrombi, (3) and possibly ulcerated atheromatous plaques (?) etc.

Mesenteric venous occlusion practically is always due to thrombosis. One case (Moloschin's) due to a retrograde embolism, has been reported. The occurrence of venous occlusion by embolism is so rare as to make the condition almost negligible. Here, again, constitutional diseases which predispose a patient to thrombosis may cause either primary closure of the mesenteric vein or terminal involvement in a descending thrombotic process. The causative agents of mesenteric venous occlusion are generally divided into four main groups:

A—Infectious: This group includes all cases in which there are infections in the region drained by the mesenteric veins; such permit penetration of the vein walls by bacteria, and the setting up of a local phlebitis, *e.g.*: appendicitis, pelvic abscess, severe enteritides, peritonitis, subdiaphragmatic abscess, perforated peptic ulcer.

B—Hematogenous: This group consists of the blood dyscrasias which so alter the constitution of the blood

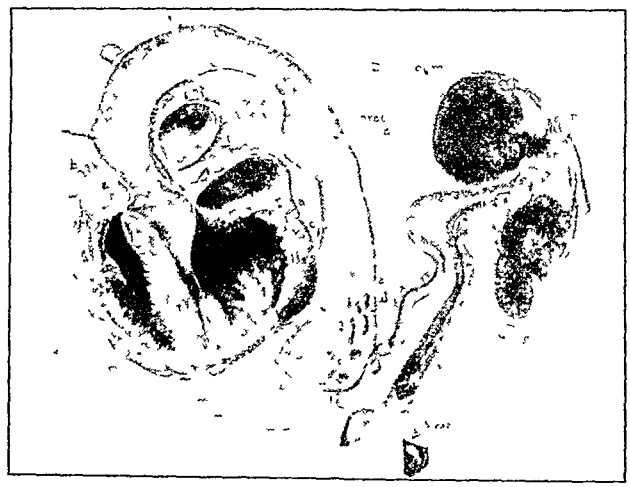


Fig. 2. Diagrammatic representation of coronary occlusion (a, b), parietal thrombi (c), thrombi in aorta (d), splenic artery embolus, infarction of spleen, and venous thrombosis.

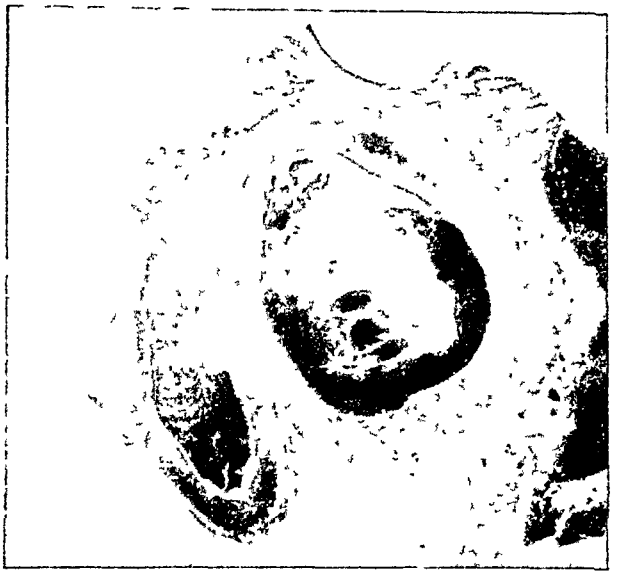


Fig. 3. Cross-section of splenic artery and vein showing embolus and thrombus in each respectively.

that there is a definite tendency to thrombus formation, *e.g.:* splenic anemias, polycythemia *vera.*

C—Traumatic: This group is comprised of those cases in which the thrombosis is the end-result of injury, *e.g.:* abdominal surgical procedures, tearing of the mesentery, rupture of a viscus.

D—Mechanical: This group, perhaps the largest, includes those cases which are due to occlusion of the veins by (1) regional neoplastic processes, (2) portal stasis caused by such entities as cirrhosis of liver, hepatitis, syphilis, cavernomatous transformation of the portal vein; (3) adhesions, (4) volvulus, (5) strangulated herniae.

PERSONAL EXPERIENCE

The Buffalo General Hospital is an institution serving both a private and ward clientele. It cares for medical and surgical cases and averages approximately 9,000 admissions per year not including those received in the Out-patient Department. Of these admissions about 58% are surgical cases.

During the years 1927-34, there were 72,409 admissions of which 44,502 were surgical patients. Mesenteric vascular occlusion was found in 17 cases The incidence of mesenteric occlusion, proven either by necropsy or by operation among the general admissions was .015%, and among the surgical admissions .025%. In the same time-period, there were 1395 autopsies; mesenteric occlusion comprised 0.6% of the necropsies. Of these, 40% were instances of arterial occlusion and 60% were those of venous occlusion.

The average age incidence of these cases was 44 years, the youngest was 20 years, and the oldest 66 years Peculiarly, in our series, males predominated in the ratio of 11-6; only in this respect did our statistical analysis exhibit a marked difference from instances recorded by other observers.

We were fortunate either in making the definite diagnosis of or in suspecting mesenteric vascular occlusion in 25% of the patients, but unfortunate in experiencing a mortality rate of 100%, whether or not the subjects came to surgery. We were unfortunate again in having no instances of spontaneous recovery such as has been reported repeatedly in the literature.

The average time duration from the onset of symptoms to hospital admission was slightly more than 54 hours. Of course, we had no way of determining how long the occlusion had been present before signs and symptoms developed.

Post-mortem observations: Of the 17 cases, 10 came to necropsy. The following is a list of the *causes of the mesenteric vascular occlusion:* arterial occlusion was caused twice by emboli originating in an aortic and mitral endocarditis; twice by emboli from mural thrombi in a fibrillating heart; and once by thrombosis associated with marked atherosclerotic changes in the wall of the superior mesenteric artery; venous occlusion was caused three times by thrombophlebitis associated with appendicitis; once subsequent to splenectomy, and once following splenic infarction, brought about by emboli carried into the splenic artery from cardiac mural thrombi. (This last case will be described in detail later).

CLINICAL PICTURE

The clinical picture essentially is alike for both arterial and venous occlusion. There are two accepted syndromes: one, *acute;* and two, *chronic* or "phlegmatic." The latter form rarely is diagnosed clinically, exhibits very vague and obscure gastro-intestinal symptoms, which to the clinician often are meaningless. It is usually associated with venous occlusion and is only recognized *in vivo,* as a rule, when, violently and dramatically, it assumes the characteristics of the acute group.

Pain is the outstanding symptom. Generally it comes on suddenly and, more often than not, without any premonitory symptoms. It is severe, lancinating, and colicky in nature at the start. It may be generalized throughout the abdomen, but frequently is localized in one area. The patient verges on complete collapse. The pulse is rapid, thready and weak. The lips are cyanotic and the extremities cold and clammy. Initially, temperature is subnormal. The patient is restless and apprehensive; he seems to realize as if by a sixth sense, that he is desperately ill. The pain may disappear only to return repeatedly in the same form; the time interval between attacks becomes less and less.

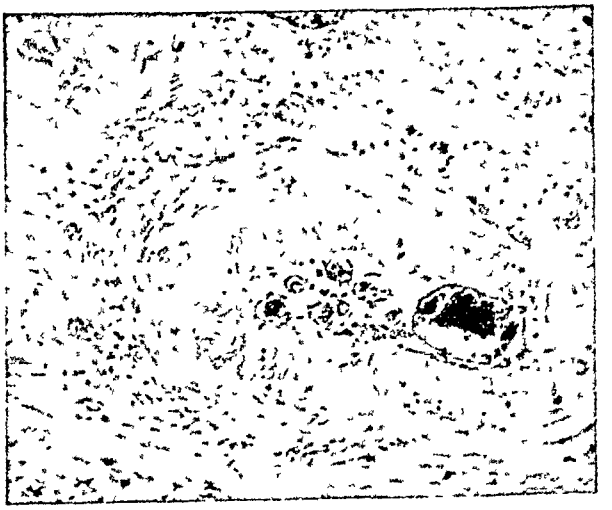


Fig. 4 Splenic artery with recanalization.



Fig. 5. Jejunum showing hemorrhagic infarction with recent thrombi in the submucosal veins.

Emesis is a quite constant sign, and at this stage is reflex. *Constipation* or *diarrhea*, or both, may occur. *Melena*, when present, indicates that some mechanism is causing serious interference with the intestinal blood supply.

At this stage, there are few *physical findings*. Generalized or localized tenderness may exist; as yet there has occurred no irritation of the parietal peritoneum and consequently there is no muscle spasm.

Very early in the clinical episode, however, a marked leucocytosis customarily is found, associated with a distinct increase in the percentage of polymorphonuclear leukocytes.

If the patient survives the initial shock, and mesenteric occlusion is neither diagnosed nor suspected, the picture rapidly progresses to one of intestinal obstruction. The pain loses its rhythmic character and becomes a constant, persistant, dull ache of peritonitis. The emesis is no longer reflex but obstructive. If bloody, it indicates a high circulatory interference involving the jejunum; it is a grave prognostic omen. At this stage, the course rapidly assumes the terminal features of intestinal obstruction and peritonitis.

Kussmaul and Gerhardt, in 1863, advanced certain postulates to aid the clinician in suspecting or actually making the pre-operative or ante-mortem diagnosis of mesenteric occlusion. These postulates are still held good:

(1)—The source for an embolus or thrombus, (2)—The presence of embolic phenomena elsewhere in the body, (3)—Melena, not to be accounted for by a primary intestinal lesion, (4)—Acute, severe, lancinating, colicky, abdominal pain, (5)—Subnormal temperature at the onset.

The *differential diagnosis* must consider the possible presence of any acute, abdominal surgical lesion; reference well may be made to the statement of Ross, in which he claims that in the majority of cases mesenteric occlusion is not a question of wrong diagnosis, but one of no diagnosis.

TREATMENT

If mesenteric vascular occlusion is to be treated intelligently it has to be diagnosed or suspected very soon after the onset of symptoms. The treatment is the same as that for any form of intestinal obstruction, *i.e.* early surgery. One point need be emphasized. No matter how critical the patient's condition appears unless the infarcted portion of bowel is removed it will terminate fatally in almost 100% of cases.

CASE REPORT

First admission 1/8/35. Service of Doctors Wright and Regan. The patient was a white male, aged 53 years, whose occupation was that of a waiter.

For the past eight months he had noticed a bluish discoloration of both feet, and that they had become progressively colder to touch. Two months before the patient inadvertently dropped a dresser drawer across the metatarsals of the left foot, and, subsequently, he was troubled with severe pain in the left foot, most marked in the fourth toe. The toe gradually assumed a darker hue and the pain became more severe. The patient consulted his personal physician, who administered a course of foreign protein therapy (typhoid vaccine); this aggravated the symptoms. On admission to our hospital the patient was unable to walk, and the foot had to be held below the level of the bed for the greatest degree of comfort.

The past history revealed a gastric hemorrhage four years ago, the etiology of which could not be ascertained and a bilateral thrombophlebitis of both lower extremities subsequent to a motor accident two years ago.

Examination: The temperature, pulse and respirations were normal. The heart was enlarged definitely to the left, and no murmurs were present. Both feet were cold and cyanotic. The fourth toe of the left foot exhibited dry gangrene. The dorsalis pedis and posterior tibial arteries were not palpable on the left leg and were barely palpable on the right.

The urine had a specific gravity of 1018, its analysis negative. The r. b. c. was 4,000,000; Hg. 80(S); color index 1. The w. b. c. was 12,500; the differential count was normal. The blood sugar was 115 mgms. and blood urea N. 11 mgms. The Kahn and Wassermann tests were negative with all antigens. Radiographic examination of the lower extremities did not reveal any evidence of calcification in the arteries.

On 1/14/35 Doctor Regan crushed the posterior tibial and superficial peroneal nerves for the sole purpose of relieving the excruciating pain. On 1/24/35 he amputated the gangrenous toe, and shortly thereafter Buerger's exercises were inaugurated. On 1/30/35 hyperemia and slight edema developed along the course of the right saphenous vein. This responded nicely to conservative treatment. On 3/3/35 the patient was discharged to the care of his private physician. All of the operative wounds had healed nicely, and there had been no pain since the nerves were crushed.

Second admission, 9/18/35—service of Doctor N. G. Russell. Since his discharge the patient had been in excellent health until approximately 4 weeks prior to readmission; at this time he began to experience constant, persistent, dull, gnawing pain, just to the left of the epigastrium; this pain was not relieved by food or alkali. On 9/7/35, about one hour after eating his evening meal, he experienced a sudden, severe, excruciating and lancinating pain in the abdomen and he collapsed. About 2 a.m. he vomited what was described as coffee-ground material. After vomiting he drank some water, but immediately regurgiated the liquid plus some blood clots. About this time he developed a bloody diarrhea. The patient required repeated ½ grain

doses of morphine for relief, and the morning of 9/8/35 was admitted to the hospital; this was approximately 15 hours after the onset of symptoms.

Temperature 100(R), pulse 140, Respirations 12.

Physical examination revealed a desperately ill patient, apprehensive, cold, clammy, and with a peculiar ashen gray cyanosis about the face. There were a few crackling rales at the bases of both lungs. The heart was very rapid, tones distant, regular; there were no murmurs. Blood pressure 104/86, (pulse pressure 18!) The abdomen was not distended, but there was marked tenderness in the epigastrium and in the left flank. At no time could muscle spasm or a mass be demonstrated. Rectal examination revealed no abnormalities.

The urine had a specific gravity of 1020; albumen and glucose were 1-plus, and the sediment revealed many w. b. cells and an occasional r. b. cell. The r. b. cell count was 5,000,000, Hg. 100% (T); the w.b.c. was 35,000, polys 93%. The blood sugar was 248 mgms.. and urea N. 41 mgms. per 100 c.c. The stool exhibited 4-plus occult blood, and was watery and grossly bloody.

The electrocardiogram was interpreted as showing no change significant of recent coronary occlusion, but definite changes referable to an old infarction.

The patient failed rapidly in spite of all the supportive therapeutic measures instituted. Death occurred 26 hours subsequent to hospital admission.

The clinical diagnosis rested between a perforating and penetrating ulcer involving the pancreas and a mesenteric thrombosis.

Necropsy findings: The autopsy was performed 30 minutes after death. The pertinent anatomical features were — total occlusion of the circumflexing branch of the left coronary artery by a completely obliterative thrombosis; marked narrowing of the oblique descending branch in the anterior wall of the left ventricle; moderate atherosclerosis of the descending anterior branch of the left coronary artery without complete obstruction; very extensive fibrous myomalacia of the left ventricle, most marked in the posterior wall, with several polypoid vegetations attached to the fibrous endocardium; distinct diffuse fibrosis of the anterior wall decreasing in severity towards the septum; so-called "diffuse wall aneurysm" of the left ventricle, especially at the anterior and posterior walls from fibrous organization of myomalacious infarcts. (Rokitansky aneurysm); distinctly dilated left ventricle; marked atherosclerosis of the lower thoracic and entire abdominal aorta; localized recent parietal thrombi at the lower end of the thoracic aorta; multiple old infarctions of the spleen, with extensive adhesions to the diaphragm; considerable atherosclerosis of the splenic artery (aneurysm serpentinum).

There were *complete occlusion of the distal portion of the splenic artery by thromb-embolus;* firm adhesions between splenic artery and splenic vein near and at the hilus; *obliteration of the distal portion of the splenic vein by an organized thrombus; more recent ascending thrombosis in the proximal part of the splenic vein; entirely recent massive thrombosis of the mesenteric vein; portal vein, and colic vein, with recent hemorrhagic infarction of the upper jejunum, and hemorrhagic necrosis of its entire wall;* very severe enterorrhagia; no hemorrhagic necrosis in lower jejunum and ileum; approximately 1,000 c.c. of thin blood tinged fluid in the peritoneal cavity.

The involved portion of the intestine measured 65 cm. and was markedly distended. The serosa presented a dusky bluish red hue, and was covered with flakes of fibrin. The bowel wall felt soggy, edematous, and was studded with many petechial hemorrhages. The normal sheen and lustre of the peritoneal coat had entirely disappeared. There were a few focal areas of necrosis, varying in size from pinhead to split pea. The arterial mesenteric system exhibited no gross involvement. The thrombosis of the portal and mesenteric veins was very recent, dark red in color and only slightly adherent to the intima. It extended into the smallest of the mural arcades on the intestinal wall. The thrombosis of the splenic vein felt firm, was grayish red in color, completely adherent to the intima, and extended directly into a large infarcted area located in the hilus of the spleen.

On serial sagittal section of the spleen, an old, firm, wedge shaped, infarct was found measuring 3 x 2.5 x 0.5 cm. beginning in the hilus of the spleen, and extending through the entire splenic structure, to the serosa on the opposite side. The apex of the wedge was situated in the hilus, and the fan shaped portion at the periphery. The splenic artery and vein, together with their associated thrombi could be traced directly into the apex of the infarcted portion of the spleen.

Splenic artery: Histologically, the intima for the most part was of average thickness. In certain localized areas, however, it was markedly thickened, apparently due to fibrous tissue. The internal elastic membrane had undergone reduplication. The tunica media was of normal width. The adventitia was composed of fibrous tissue, and in sections examined was not adherent to the vein. It contained a few scattered lymphocytes. The lumen was practically entirely filled with thromb-embolus composed chiefly of fibrin, red blood cells, and a very few leukocytes. In one area it was adherent to the intima, and here the endothelium was deficient. The thromb-embolus exhibited a focal area of organization. No evidence of a tuberculous or leutic arteritis could be demonstrated.

Spleen: Typical anemic infarction with beginning organization and reactive inflammation.

Splenic vein: The vein was completely occluded by an adherent thrombus made up of fibrin, red blood cells, and leukocytes. The wall appeared not remarkable. There was no evidence of a phlebitis.

Intestine: Practically complete necrosis of the mucosa and submucosa was present with small isolated areas of desquamation. The mucosal and submucosal vessels were markedly injected. Distinct recent hemorrhages were visible in the mucosa and submucosa. Submucosal veins showed recent thrombi, composed of fibrin, red cells, and leukocytes. Surrounding the veins was a distinct leukocytic infiltration. The entire picture was that of hemorrhagic necrosis with recent venous thrombosis.

SUMMARY

A case of mesenteric venous occlusion subsequent to infarction of the spleen is reported.

This case seems worthy of recording, not alone because of the symptomatology, but because of the sequence of etiologic factors concerned in the production of the pathologic lesions which were demonstrated post-mortem. Two sources manifest themselves as a possible origin of the thromb-embolus demonstrated in the splenic artery with the production of an anemic infarct located at the hilus of the spleen. (1), the polypoid vegetations found at autopsy clinging to the fibrous endocardium, and (2), the parietal thrombi situated in the lower third of the thoracic aorta. We feel that based merely on the incidence of occurrence, the most likely site of the two was in the heart. Since it is a proven fact that infarction of any tissue will produce thrombosis in the veins and the splenic vein was proved both grossly and histologically, to have its origin in the infarcted area, it is proper to assume that the original embolus causing the splenic infarct also was indirectly the cause of the thrombosis in the splenic vein. Also we feel that the terminal, mesenteric, venous occlusion definitely was a descending thrombotic process of some duration, as evidenced by

the gross and histologic appearance of the thrombus *in different areas of the vein.*

Bacterial stains (Gram and methylene blue), did not reveal the presence of any organisms in either the splenic artery or vein. Careful macroscopic and microscopic studies for a specific arteritis or phlebitis (tuberculous or syphilitic) as the causative agents in the production of the thrombosis were negative. As far as we are able to determine the splenic vein thrombosis was not due to adhesions between the artery and vein which may have formed after the throm-embolus occurred in the splenic artery.

A careful search of the literature revealed many cases of mesenteric, vascular occlusion, with incidental findings of infarctions in the spleen, or splenic vein thrombosis with a subsequent descending thrombosis of the mesenteric vein. However, the only case which we discovered in which mesenteric occlusion is a direct result of a splenic infarction, was one reported by L. T. Webster in 1921. This was a 45 year old man, who had a penetrating ulcer of the stomach with perforation into the splenic artery with a resultant thrombosis of this artery followed by massive infarction of the spleen, and terminally, a complete descending thrombosis of the portal system initiated in the splenic vein. We were unable to find record of any proved report in which the thrombosis of the splenic vein was due to a splenic infarction having as its source a thrombo-embolus originating in the heart, and lodging in the splenic artery.

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SECTION II—*Experimental Physiology*

An Investigation into the Production of a Proteolytic Ferment in the Duodenum which will Increase the Anti-anemic Efficacy of Liver; Its Relationship to the Cause of Pernicious Anemia*

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THE theory that pernicious anemia is due to the absence in the stomach of an intrinsic gastric factor, probably a proteolytic ferment, has received wide acceptance, but has seemed inadequate to the minds of a number of investigators (1, 2, 3, 4). The experiments herein described by the author apparently demonstrate the presence of this factor or ferment in the duodenal mucosa in a concentration equal to or greater than in the gastric mucosa. Proof of its presence in the small intestine would greatly alter the present concept of the etiological factors contributing to the cause of macrocytic hyperchromic anemias.

A vast amount of recent experimental work has led to the following explanation for the development of pernicious anemia, which has been widely accepted despite the recent report of Greenspon (5) to the contrary. Briefly, certain elements of the diet, notably muscle and organ tissue, supply a source of material which can normally be digested in the stomach to produce a substance necessary for the maturation of red blood corpuscles. Castle has called this part of the diet the extrinsic factor. He has named the digesting agent or unknown proteolytic ferment the intrinsic gastric factor. The substance produced by the interaction of these two factors may be termed an anti-anemic substance or maturation substance. The extrinsic factor is contained in most meats which are injested, particularly beef muscle, and in yeast preparations. Liver is an extremely rich source of this factor. The intrinsic factor has heretofore only been demonstrated in the gastric juice and the gastric mucosa. It is characteristically absent in pernicious anemia, or greatly diminished in amount (6). Consequently the necessary maturation substance is not formed and anemia results. However, this maturation substance

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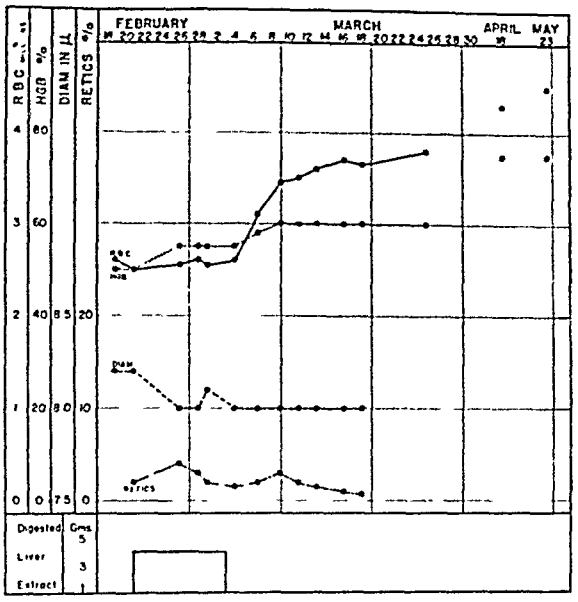


Fig. 1. Improvement of the anemia in Case II following the daily administration of one vial of liver extract No. 343 which had been incubated with 0.5 grams of duodenal mucosa.

is present in large amounts in liver, stomach and other organs, so that the oral or parenteral administration of these tissues or their extracts is highly effective in the treatment of pernicious anemia.

According to this theory anemia may come about in one of at least four ways. First, a diet deficient in the extrinsic factor will cause a macrocytic hyperchromic anemia as described in India (7), or as has been experimentally produced in pigs (8). Second, spontaneous absence of the intrinsic factor in the stomach will cause pernicious anemia; this is Castle's theory, but it is well recognized that if the source of the intrinsic factor is removed by gastrectomy in either man or experimental animals pernicious anemia does not develop except in a few very rare instances in man. Third, even if the maturation substance is present in the gastro-intestinal tract in adequate amounts it may not be absorbed and this is what occurs in severe dysenteries or possibly in sprue. Fourth, this maturation substance may be absorbed from the gastro-intestinal tract, but may not be utilized by the hematopoetic system. We are concerned here with only the second possibility, namely the absence of the intrinsic gastric factor. If this were the basic cause of pernicious anemia it is hard to see why spontaneous remissions occur and why after a remission has been induced a patient may not relapse for a year or more without any further treatment. Even more difficult to explain is the fact that gastrectomy does not ordinarily produce hyperchromic anemia, and that if it does the anemia does not appear until years after the operation.

In 1933, Kühnau (9) carried out a number of feeding experiments which suggested that the intrinsic factor was present in the duodenal secretion. As he employed a mixture of gastric and duodenal contents his work is not very convincing. In 1930 the Author carried out a somewhat similar feeding experiment incubating an average of 50 c.c. of duodenal contents daily with the juice pressed from one pound of beef steak. No special precautions were taken to try and prevent gastric contents from diluting the duodenal fluid. This mixture was made just alkaline to litmus and kept at 37° C. for one hour. It was fed daily for five days to a woman with severe pernicious anemia. An astonishing clinical improvement occurred, and the R.B.C. count rose from 1,060,000 to 1,660,000 and the hemoglobin from 30% to 44% within one week. The reticulocytes rose from 0.5% to 14% on the seventh day. She felt so well she declined further treatment. Although this patient must have received some gastric as well as duodenal secretion, the amount of duodenal contents used was less than that ordinarily required for successful incubation when pure gastric contents is employed. This fact together with the very rapid improvement in this patient's condition indicate that a ferment of high digestive activity may be present in the duodenal contents.

In 1935, Meulengracht (10) showed very clearly that the duodenum contained the same anti-anemic substance as stomach and he thought from his careful microscopic studies of the pyloric and duodenal glands that the duodenal mucosa might secrete the intrinsic factor. To prove its presence or absence is not simple. The difficulties of procuring pure duodenal secretion are obvious. It was felt that the most ready approach to the problem was to test the digestive powers of the duodenal mucosa on liver or liver extract in the same way that the digestive power of stomach mucosa is tested. It is now well recognized that when liver is incubated with gastric juice or with gastric mucosa its potency as an anti-anemic agent is increased several fold, and this is explained by the action of the intrinsic factor of the stomach on the extrinsic factor in the liver producing much more of the anti-anemic substance than was contained in the liver before incubation (11, 12). Exactly this principle is used in the preparation of Extralin by the Eli Lilly Company, cutting down the necessary daily liver extract ration to about one-third of what had been required previously. Fouts, Helmer and Zerfas (13) emphasized the advantages of using a small amount of a standardized liver extract as the source of the extrinsic factor in-

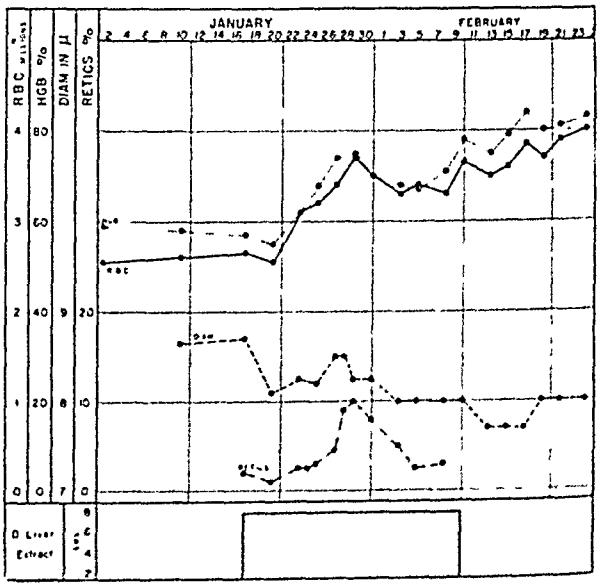


Fig. 2. Improvement of the anemia in Case VI coincident with duodenal liver extract therapy.

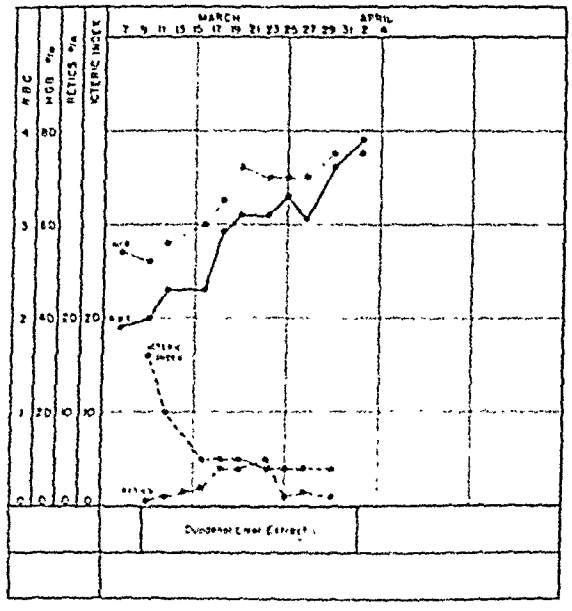


Fig. 3. Rapid improvement of the anemia and disappearance by hyperbilirubinemia in Case VII when treated with duodenal liver extract.

stead of beef muscle, Vegex or some other substance, the potency of which may vary to an unknown degree. They used the contents of one vial of Lilly's Liver Extract No. 343 which is the primary anemia fraction in powdered form derived from 100 Grams of whole liver. Its weight is approximately 4.5 Grams. The usual therapeutic dose of this extract is four to six vials daily when treating a patient with pronounced anemia, while one to two vials daily (4.5 to 9 Grams) are without beneficial effect. The presence of the intrinsic factor in a given amount of gastric juice or gastric mucosa may then be tested by incubation with one vial of the liver extract in solution and the resultant product fed daily for ten to twenty days to an anemia patient in relapse. If an average reticulocyte response and increase in red cells occur at a given erythrocyte level the intrinsic factor is present in sufficient amount for the quantity of gastric juice or mucosa used.

In the first group of the Author's feeding experiments two patients were treated. One vial of liver extract No. 343 was placed in 75 c.c. of 0.2% sodium bicarbonate solution to which 5 c.c. of a similar solution containing 0.5 Grams of human duodenal mucosa was added. This mucosa was secured by scraping normal duodenums obtained at autopsy after they had been resected and washed free of intestinal contents. This was carried out as soon after death as possible and the scraping put in the dilute alkaline solution in a beaker and kept in the ice box until ready for use, which was usually twenty-four hours but sometimes longer. As a rule the scrapings from two or more duodenums were prepared at the same time and mixed together. The duodenal mucosa liver extract mixture was incubated for one hour at 37°, and then placed in the ice box a few hours and administered cold. Two days doses were prepared simultaneously, the second dose being kept in the ice box over night.

In the second group of experiments the duodenal mucosa of the hog was incubated with liver in exactly the same manner as Extralin is prepared (12) except the duodenum was used instead of the stomach. I am indebted to the Eli Lilly Company for the preparation of this extract which contains approximately equal parts of powdered liver and mucosa. It was placed in capsules to facilitate its administration, each capsule containing approximately two-thirds of a gram of the powder.

FEEDING EXPERIMENTS. GROUP I

Case I. S. L. D., a 70 year old single male rapidly developed a severe anemia without gastro-intestinal or nervous system symptoms in the Summer of 1935. He had a moderate hypertension and had been under treatment for a diverticulum of the bladder with a low grade cystitis for several years. Two blood counts in 1932 were normal. His tongue showed no atrophy of the papillae. The spleen was not palpable. The deep reflexes and sensory discrimination over the lower extremeties were normal. The stool was negative. Gastric analysis showed achlorhydria to histamine. Complete gastro-intestinal X-ray studies were negative. Urinalysis was negative except for a few pus cells. The blood urea was 32 mgs. per 100 c.c. of blood. The R.B.C. count was 2,420,000 and the hemoglobin 43%. The average diameter of the erythrocytes was 8.1u. and the average volume was 115.2 cu.u. Although the color index was below one (0.9) a tentative diagnosis of pernicious anemia was made based on the macrocytic anemia with achlorhydria in an old man without any other obvious cause for an anemia. He was given 75 c.c. of a solution of one vial of Lilly's liver extract No. 343 incubated with 0.5 Grams of fresh duodenal mucosa daily for nine days; and again subsequently for a second period of fifteen days, although this period was interrupted for four days. The blood findings in relation to therapy are shown in Table I. As he was ambulatory and irregular in his attendance to the laboratory it was not possible to make as frequent and detailed blood studies as were desired.

Comment on the Results of Therapy. At the end of the first period of treatment the patient had gained 730,000 R.B.C. in nine days from an original level of 2,420,000 and the hemoglobin increase was 17%. Two weeks later without further treatment the total gain in R.B.C. for the twenty-three days was 1,210,000, and there was a further increase in hemoglobin of 5%. The blood count quickly fell and the color index rose to 1.2. During the second period of treatment the R.B.C. count rose 1,200,000 cells in three weeks, and the hemoglobin rose 7%. The average diameter of the cells was little altered. Four months later after taking liver extract and iron very irregularly the R.B.C. count was 4,210,000 and the hemoglobin 78%.

Case II. J. McD., a 62 year old single male indigent entered the hospital for the second time on Feb. 12, 1935, complaining of weakness. At his first entry a year previously he presented the classical picture of pernicious anemia with macrocytic hyperchromic anemia, hyperbilirubinemia, achlorhydria to histamine and neurological findings typical of subacute combined sclerosis of the spinal cord. He responded very satisfactorily to parenteral liver therapy with reticulocytosis and increase in red blood cells and hemoglobin. He received no maintenance liver therapy.

At the last entry the red cell count was 2,570,000, and the hemoglobin 50%. The average diameter of the erythrocytes was 8.2 u. and the average volume 128.4 cu.u. He was placed on the same form of treatment as was carried out in Case I, which he received for ten days. The effect on the blood picture is shown in Table I* and Fig. 1. He received no further antianemic treatment and five months later on July 10th was ambulatory and the red cell count was 4,550,000. The hemoglobin was 78% and the average diameter of the erythrocytes was 7.6 u.

*Omitted by the editor for sake of brevity.

Comment on the Results of Therapy. This patient's reticulocytes rose to 4% on the sixth day of treatment and gradually diminished during the next two weeks. The red cell count and hemoglobin per cent were stationary during the ten day period of treatment, but began to rise four days later. The number of red corpuscles then increased in twelve days from 2,590,000 to 3,690,000, a gain of 1,100,000 cells; and the hemoglobin rose 5%. The average diameter of the erythrocytes was diminished from 8.2 u. to 8.0 u. The blood count and hemoglobin per cent subsequently rose to normal, although no further liver extract was given.

FEEDING EXPERIMENTS. GROUP II

Case III. J. J. K., a 51 year old unemployed laborer was seen on Nov. 1, 1935, in a hospital outpatient clinic complaining of weakness and difficulty in walking. He had previously been in the County Hospital with severe pernicious anemia and moderately advanced subacute combined sclerosis of the spinal cord. He had shown a characteristic and rapid response to parenteral liver therapy and for some months after leaving the hospital had eaten some liver almost daily. He had taken no liver at all during the past six weeks. He walked with a spastic ataxic gait and had considerable pain in the left leg. He appeared ruddy but the R.B.C. count was only 3,570,000 although the hemoglobin was 75%. The average diameter of the erythrocytes was 8.1 u. and the average volume 129 cu.u. He was told to take four capsules of the duodenal liver extract three times a day and report regularly for blood counts. Unfortunately he appeared at the laboratory very irregularly, but the few blood counts made during the six and one-half weeks of treatment are recorded in Table II and show very well the marked improvement which occurred, which was also readily manifest clinically.

Comment on the Results of Therapy. This patient's red cell count was stationary at 3,600,000 cells for eleven days before treatment and for the first eleven days afterwards. During the next seventeen days it rose to 4,310,000, a gain of 710,000 cells. The hemoglobin also rose 10%. Some three weeks later and a week after treatment was stopped the red cell count was 5,310,000, a gain of another 1,000,000 cells, and the hemoglobin had reached 104%. Actually the patient gained 1,700,000 red cells and 29% hemoglobin in fifty-four days.

Case IV. Miss E. B., a 33 year old single school teacher, first came under medical observation in San Francisco on Dec. 9, 1935. Her home had previously been in the middle West where she had twice been extremely anemic in the last two years. Each time she improved rapidly on liver therapy. She was anemic again and also showed slight jaundice. Her tongue was smooth at the edges. A histamine gastric test meal revealed an achlorhydria. The R.B.C. count was 3,290,000 and the hemoglobin 80%. The color index was 1.2. The average diameter of the erythrocytes was 8.0 u., and a Price-Jones curve showed a shift to the right typical of pernicious anemia. The mean corpuscular volume of the erythrocytes was 124.6 cu.u. The icteric index was 15 units. She was treated with duodenal liver extract capsules receiving nine daily for three weeks. The favorable effect on the blood picture is shown in Table II.

TABLE I

Group 1. The effects of daily treatment of pernicious anemia with 4.5 gms. of liver extract incubated with 0.5 gms. of duodenal mucosa

Case No.	Date 1935	Day of Treatment	R.B.C. (million per cm.³)	Hgb. (%)	Average Diameter in u.
I	7-24		2.42	43	8.1
	7-27	1st	—	—	—
	8-1	6th	3.15	50	8.1
	8-4	9th	—	—	—
	8-5		3.17	60	8.1
	8-13		3.65	65	8.1
	8-19		2.87	68	7.9
	8-28		2.65	65	8.0
	8-30	1st	—	—	—
	9-4	6th	3.30	65	8.0
	9-6	8th	3.57	65	8.0
	9-10	12th	3.64	66	8.0
	9-13	15th	3.85	72	8.1
	9-18		3.88	70	7.9
	9-30		3.76	65	8.1

Comment on the Effect of Therapy. The red cell count increased by approximately 800,000 cells in less than three weeks reaching a normal level, and although the hemoglobin was already 80% it rose 5% higher. The average diameter of the erythrocytes diminished from 8.0 u. to 7.8 u. The icterus index fell from 15 units to 8 units. Her clinical improvement was striking.

Case V. T. F., a 56 year old Mexican housewife had been under hospital observation for six years on account of pernicious anemia, and all the hospital records were available for study. She had suffered six relapses before her present hospital entry. Two of these occurred while she was on a liver diet, and she always relapsed quite promptly when she ate no liver. On two occasions a liver diet containing 200 Grams of liver daily failed to produce a remission. On one occasion 2 c.c. of Lilly's Parenteral Liver extract injected daily for three weeks failed to produce any appreciable reticulocyte response or any increase

in red cells or in hemoglobin. Large doses of concentrated liver extract administered parenterally invariably instigated a typical and complete remission.

On Dec. 12, 1935, her anemia was severe. There were 1,250,000 R.B.C. and 24% hemoglobin. Therapy with duodenal liver extract capsules was started on Dec. 17, 1935. She received nine capsules daily but did not always swallow all of them. The relation of this treatment to the blood picture is shown in Table II.* It was continued for ten days only, when daily parenteral liver treatment was substituted as the patient's condition became very unsatisfactory. The blood count then began to improve and the reticulocyte count rose to 36% after the fifth injection of 10 c.c. of concentrated liver extract.

Comment on Results of Therapy. No definite response to the duodenal liver extract therapy was demonstrable in this short experiment, but it should be emphasized that this patient had previously failed to respond to oral liver therapy, and that the amount of duodenal liver extract she received by mouth was not large. However, it is noteworthy that during the ten days of the experiment that the icteric index fell from 15 units to 8 units, and that the subsequent rise in reticulocytes and number of R.B.C. may have been due in part to the oral therapy.

Case VI. E. P. T., a 53 year old housewife first came under observation in January, 1936, complaining of weakness. In the past eighteen months she had twice been in the County Hospital with anemia. She had responded slowly but definitely to liver therapy. Obesity and myocarditis were noted. At present her blood showed the characteristic findings of pernicious anemia. The R.B.C. count was 2,550,000 and the hemoglobin 59%. The color index was 1.2. The Price-Jones curve was typical of pernicious anemia with an average diameter of 8.65 u. The average volume of the erythrocytes was 130.8 cu.u. The icteric index was eleven units and the direct van den Bergh was negative. Gastric analysis revealed an achlorhydria to histamine. Gastro-intestinal X-rays showed nothing abnormal.

The blood count remained practically stationary for three weeks. Treatment was started on Jan. 17, consisting of four capsules of the duodenal liver extract t.i.d. The relationship of therapy to the blood picture is shown in Table II* and Fig. 2. Treatment was discontinued after twenty-three days, but the blood count was followed for two weeks longer.

Comments on the Results of Therapy. There was a gain of 1,150,000 R.B.C. and 20% hemoglobin by the 12th day of therapy, and the reticulocytes reached 10% on that day. Five weeks after the instigation of therapy the R.B.C. count had risen from 2,550,000 to 4,010,000 and the hemoglobin from 55% to 83%. The average diameter of the R.B.C. fell from 8.7 u. to 7.7 u. with a rise to 8.u. after the cessation of treatment. The icteric index had fallen from an initial 11 units to 7 units after three weeks. This rapid improvement of the blood picture to normal was accompanied by a marked clinical improvement. The patient was bed ridden at first, but was able to walk out of the hospital in six weeks.

Case VII. Mrs. D. S., a 54 year old Irish housewife was referred on March 7, 1936, by Dr. J. M. Meherin for the treatment of pernicious anemia. She complained of weakness, difficulty in walking and sore tongue. She was pale and slightly jaundiced. The tongue was atrophic. There were several abscessed teeth. The vibratory sense was lost over both lower extremeties. The red cell count was 1,900,000, the hemoglobin 54% and the color index 1.42. The average diameter of the erythrocytes was 8.6 u.

TABLE II

Group 2. The blood findings in pernicious anemia treated with duodenal liver extract

Case No.	Date 1935	Day of Treatment	R.B.C. (million per cm.³)	Hgb. (%)	Average Diameter in u.	Icteric Index
III*	11-1		3.57	74	—	—
	11-12	1st	—	—	8.1	9
	11-14	3rd	3.66	—	—	—
	11-23	12th	3.60	85	—	—
	12-10	29th	4.31	95	—	—
	12-26	55th	—	—	—	—
	1-3-36		5.31	104	7.7	5
IV**	12-10		3.29	80	8.0	15
	12-12	1st	3.34	80	8.0	—
	12-16	5th	3.41	78	8.0	—
	12-18	7th	3.73	78	8.0	—
	12-20	9th	3.84	78	7.9	—
	12-23	12th	3.88	80	7.8	—
	12-27	16th	3.78	80	7.9	—
	12-30	19th	4.10	85	7.8	8
	1936 1-1	21st				
	1-2		3.99	85	7.8	—
	1-9		4.07	83	7.8	—

*Patient Received 8 Gms. Daily.
**Patient Received 6 Gms. Daily.

*Omitted by the editor for sake of brevity.

*Omitted by the editor for sake of brevity.

and the Price-Jones Curve showed a number of very large macrocytes. The average volume of the erythrocytes was 152.3 cu.u. The icteric index was 16 units. A gastric achlorhydria was reported by a physician who had seen her several years previously. She was forthwith placed on nine capsules of duodenal liver extract daily, and marked clinical improvement was soon evident. The rapid changes in the blood picture for the better are recorded in Table II* and Fig. 3.

The red cell count rose from just below two million to just below four million during twenty-four days of treatment. The hemoglobin per cent increased from 54% to 75%. The reticulocyte response reached a peak at 5.3% on the fourteenth day at the time there were three million red cells. The marked macrocytosis of the erythrocytes was reduced from a maximum of 8.9 u. to 8.2 u. The serum bilirubin fell to normal within the first week.

COMMENT ON THE EFFECT OF THERAPY

An analysis of the effects of treating these seven cases of pernicious anemia with small amounts of liver extract which had been incubated with duodenal mucosa reveals that six of the seven patients were benefited not only clinically, but also the blood picture improved markedly. In the one case recorded as a failure there seems to be sufficient reason aside from inadequate therapy why no improvement occurred. This is discussed in the protocol of Case V. In five of the cases there was an increase of one million or more red cells within three weeks and in four instances a gain of the same magnitude took place during a period of ten to twelve days. This improvement is all the more striking in that only one of these patients, Case VII, had an initial erythrocyte level under 2,500,000; as the less anemic patients ordinarily improve more slowly. In Case VII with an initial erythrocyte level of less than 2,000,000 red cells there was a rapid gain of approximately 2,000,000 cells in three and one-half weeks. In one instance, Case IV, there was a gain of only 800,000 red cells in three weeks, but this patient presented only a moderate diminution in the number of erythrocytes and the hemoglobin was normal. Actually her improvement was very satisfactory for the degree of anemia present.

The reticulocytes were studied in three of the six cases successfully treated and in each case there was an increase in their number to a maximum per cent corresponding to the expected average (14). In two of these patients, Cases VI and VII, there was a marked increase in the number of red cells previous to the time the highest per cent of reticulocytes occurred, and in two other patients Cases I and IV, a similar increase occurred before the time when the reticulated cells would ordinarily be expected to reach their peak. In each of these four patients a latent period of seven to ten days occurred following the initial rapid increase in the number of erythrocytes during which time no further increase in their number took place. A study of Tables I and II and Figs. 2 and 3 strongly suggests that an early complete maturation of erythrocytes developing in the bone marrow has preceded the appearance of large numbers of reticulocytes in the circulating blood. This is contrary to the usual sequence of events which takes place under standard forms of treatment. Its exact significance cannot be analyzed until further cases are studied.

On the whole the changes in the average diameter of the erythrocytes conform closely to those occurring under the usual liver and stomach therapy (15). The degree of macrocytosis was reduced in each instance except in that of Case V. The serum bilirubin concentration as measured by the icteric index was reduced to the normal range in each of the five cases in Group II including Case V. The icteric index was not studied in Group I. The rapid reduction in serum bilirubin which occurred in Case VII is shown graphically in Fig. 3 and indicates an excellent response to therapy (16).

The amount of duodenal liver extract used in treating these patients varied slightly, but was probably comparable with the amount of Extralin which would have been prescribed. It was always less than the amount of liver extract No. 343 which Minot (17) gives as the minimum which will produce a satisfactory response. In Group I the therapy differed from Group II in certain respects which are worthy of note. In this smaller group of two cases human duodenal mucosa was used which might contain a more concentrated amount of the unknown digestive enzyme than is present in the duodenum of the hog. This is suggested by the fact that the proportion of mucosa to liver used might be calculated as one to two hundred, as 0.5 Grams of mucosa were incubated with the liver extract derived from 100 Grams of whole liver. In the second group the proportion was about one to one, but incubation was carried out with fresh liver concentrate instead of just the dried primary anemia fraction. In the preparation of Extralin the proportion of hogs stomach used is also about one to one, but an adequate digestive reaction has not been reported if the proportion falls below one to twenty (18). This suggests the possibility that the unknown enzyme is at a higher concentration in the duodenal mucosa than in the stomach. Such an assumption is supported by the results obtained from feeding two patients, with hyperchromic macrocytic anemia, only three capsules (2 Grams) of duodenal liver extract daily. One of these patients suffered from a hepatitis, and the cause of the anemia was not determined in the other. A pronounced clinical and hematological improvement occurred in each. Also it must not be overlooked that successful therapy in all the patients treated with the duodenal liver extract might conceivably have been obtained from the presence of the liver extract alone, but this would seem most unlikely, as the incidence of satisfactory improvement following the administration of such small amounts of liver extract is extremely low. Further experiments are necessary positively to clarify this important point.

The presence of Castle's intrinsic "gastric" factor in the duodenum in a concentration equal to or greater than that in the stomach must alter the conception that the fundamental cause of pernicious anemia is a gastric defect. It seems probable that the presence or absence of this gastric factor would have no definite bearing on the development of pernicious anemia as long as there was an adequate production of the unknown ferment in the upper small intestine. This is best illustrated by the well known fact that total gastrectomy very rarely produces pernicious anemia, and then only in man. In the few cases in which it ap-

*Omitted by the editor for sake of brevity.

pears as a late sequel it may be due to gradually developing atrophy of the duodenal mucosa brought about by changes in the normal physiological functions in this region which such an operation might well incur. It is likely that in pernicious anemia there is ordinarily a combined gastro-duodenal defect, or as Meulengracht has termed it, an atrophy or inactivity of the pyloric gland (Brunner's glands) organ (10). The absence of pernicious anemia in many cases of gastric achylia with atrophy of the mucosa would also be explained. Whether an inability to produce this ferment in the duodenum could be compensated for by its production in the stomach cannot be decided at present, but is of the utmost interest in relation to sprue as in this disease the blood picture of typical pernicious anemia may develop with the presence of Castle's intrinsic factor in the stomach (19).

The results of the experiments recorded in this report naturally give rise to many other interesting questions concerning the etiology of all the macrocytic hyperchromic anemias which it would be premature to consider at present except on a theoretical basis. However, the possibility of this unknown ferment being related to enterokinase and its production in the jejunum or ileum as well as in the duodenum must be considered.

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Histidine in Experimental Gastric Ulcer*

By

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HISTIDINE hydrochloride was introduced by Weiss and Aaron (1) in 1933 for the treatment of peptic ulcer in man. In their investigation on dogs they used the Mann and Williamson (2) operation for the production of peptic ulcer, the principle of which is the diversion of alkaline duodenal, pancreatic and biliary secretions into the terminal ileum. As a result, protein digestion to the amino acid end stage, is interfered with. They concluded that deficiency of the essential amino acid, histidine, was responsible for the ulcer formation, since substitution therapy of histidine by injection prevented the occurrence of these lesions.

In this country, Volini and McLaughlin (3) produced gastric ulcers in rats by giving histamine parenterally and by enemata. In their report they state that these ulcers did not occur, when the animals were protected by previous injections of histidine.

Fontes and Bauer (4) repeated the experiment of Weiss and Aaron substituting oral administration of histidine for the parenteral method, and reported ulcer prevention in only 30% of the animals. They questioned whether the lack of histidine is the sole factor in the production of experimental ulcer.

Ivy (5) questions the basis of histidine-deficiency-theory. He believes "Weiss and Aaron did not 'run' their Exalto-Mann Williamson dogs long enough." Recently Sandweiss, Saltzstein and Glazer (6) performed the Mann-Williamson operation on twelve dogs in an attempt to repeat the experiment of Weiss and Aaron. They found that the animals developed ulcers even though they received daily histidine injections. Flood and Mullins (7) found that 6 out of 11 dogs re-

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TABLE I

Group	Number of Rats	Feeding	Fluids	Injections	Results	Percentage
A	15	Fasting for two days Steenbock Bills Diet and fresh vegetables on third day.	2% pepsin and 0.3% HCl	Daily ½ c.c. Histidine	14 animals had ulcers	93%
B	15		2% pepsin and 0.3% HCl	None	14 animals had ulcers	93%
C	10		Water	Daily ½ c.c. Histidine	5 animals had ulcers	50%
D	20		Water	None	None	0

ceiving daily injections of histidine monohydrochloride after surgical duodenal drainage developed ulcers.

Our present investigation was undertaken to evaluate the efficacy of histidine monohydrochloride in the prevention of experimental gastric ulcer in the rat. Our previously described method of ulcer production (8, 9), based on the feeding of pepsin-hydrochloric acid, was employed in a somewhat modified form. A 2% solution of commercial pepsin (1:10,000 Parke, Davis & Co.) in 0.3% hydrochloric acid, instead of the originally described 20% solution was found equally effective.

EXPERIMENTAL

Sixty rats of the original Wistar strain, averaging four months in age were used in this experiment. The animals were divided into four groups as shown in Table I. The rats in all the groups were fasted for two days and fed the Steenbock Bills (10) stock diet with fresh lettuce and sliced carrots on the third day, in recurrent cycles for a period of sixteen days. Stoppered flasks containing a 2% solution of pepsin (1:10,000 Parke, Davis & Co.) and 0.3% hydrochloric acid were attached to the cages of groups A and B so that the animals could partake of these solutions ad lib. In groups C and D a continuous supply of water was available. In groups A and C the rats received daily injections of 0.5 c.c. of histidine monohydrochloride (Larostidin-Hoffman La Roche, Inc.) for nineteen days. Three of these injections were given prior to the onset of the experiment. To prevent leakage, the point of injection was sealed with collodion.



Fig. 1. Microscopic appearance of section of experimentally produced ulcer of the rat's stomach.

RESULTS

At autopsy, the pepsin hydrochloric acid group (A) that had received 19 daily injections of histidine revealed an incidence of about 93% of multiple gastric lesions of the pro-stomach. The incidence was equivalent to that of the pepsin hydrochloric acid group (B) that had received no histidine injections.

Autopsy findings in group (C) which received no pepsin hydrochloric acid mixture with daily injection of histidine disclosed that 5 of 10 rats (50%) had multiple gastric lesions. A control group (D) under a similar regime without histidine injections developed no gastric lesions.

The lesions had raised margins and umbilicated centers. The gross and microscopic picture (Fig. 1) of submucosal edema, cellular infiltration with varying degrees of desquamation and mucous membrane erosion in the rats which received histidine injections, was similar to that previously described (8, 9).

DISCUSSION

Histidine monohydrochloride is being subjected to universal trial in the treatment of peptic ulcer in man. Its use is based upon the histidine-deficiency-theory of Weiss and Aaron and on their reports in animal investigation.

The recent clinical investigations of Sandweiss, Martin, Flood and Mullins in the use of histidine in the therapy of peptic ulcer are not in full accord with the earlier favorable reports of foreign and American investigators. The original work of Weiss and Aaron on dogs has not been confirmed by other investigators. Recently, the value of histidine in prevention of experimental gastric ulcer in the dog has been questioned by Ivy (5) and Sandweiss, et al (6). The favorable reports of Volini and McLaughlin in preventing ex-

perimental gastric ulcer in the rat with histidine injections was not confirmed by our investigation. We found the incidence of gastric lesions identical in the groups on the ulcer producing regime, with and without histidine injections.

The high incidence (50%) of gastric lesions in group (C) in which no ulcer producing agent was employed appears to have followed the histidine injections. These ulcers may have been produced by a resultant histamine formation (11), since histidine may be converted by simple decarboxylation into histamine (12). Whether histidine parenterally administered in man, could through a similar conversion adversely influence a gastro-duodenal defect is a subject for future investigation.

SUMMARY

1. Experimental gastric ulcers in the rat were produced by our pepsin-hydrochloric acid method.

2. Daily injections of histidine monohydrochloride (Larostidin-Hoffman La Roche) were not effective in preventing experimental gastric ulcers.

3. A high incidence of gastric ulcers subsequent to injections of histidine were observed.

4. The conversion of histidine into histamine is suggested as a possible experimental ulcer producing mechanism.

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Studies in Bowel Drainage

By

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IF glucose is given in quantities in excess of 2 grams per hour, the blood sugar level rises and sugar appears in the urine. It has been believed that starch in any quantity is completely hydrolyzed (to sugar) and absorbed. However, when given in large quantities, starch does not effect the blood sugar level; does not appear as sugar in the urine; nor does it appear in the feces as starch or sugar.

It has been believed that the reason why starch does not act like sugar in the gastro-intestinal tract is because starch is often bound up in vegetable or fruit cells and is but slowly absorbed. But preliminary studies indicated to us that ingested starch has a twofold fate: part of it—that part which comes within the amylolytic threshold—is absorbed into the blood stream as sugar, while the remainder—the excess which cannot be hydrolyzed by the available enzymes during its passage through the upper bowel—passes to the colon, where it becomes the determining factor in the mechanism of normal bowel drainage.

Cannon long ago advanced the hypothesis that the motor mechanism of the bowel depends upon bulk: when the bowel is distended to the "just right" pressure, the intestinal muscles contract, thereby forcing onward the bowel contents. This observation was the basis of the former widespread use of bran and other indigestible bulky substances.

It is true that coarse, bulky roughage stimulates the motor mechanism of the bowel, but this stimulation results from the mechanical irritation caused by large unbroken particles contained in the feces. It is a common datum of observation that irritating roughage, bran for example, often overstimulates the bowel musculature, thereby producing constipation of the spastic type. This observation would seem to indicate that mere bulk or roughage is not the factor concerned in the mechanism of normal bowel drainage.

Schmidt long ago pointed out that there is no distinguishable difference between a "good drainage" stool and a "constipated" stool, although macroscopically and clinically they are as different as day from night. Schmidt believed that constipation resulted because the digestive enzymes did their work too well, so well that little food bulk remained to stimulate the bowel. Our observations indicate that mere bulk as such, is unimportant, but that the colloidal state in which the feces is dissociated is the determining factor which controls normal drainage. Because he believed, erroneously, that ingestion of different foods causes differences in feces, Schmidt introduced his test diet as a starting point, whereby feces of a uni-

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form composition, a normal stool, would be produced. Our observations indicate that normally, feces is always of a uniform composition, irrespective of the kinds of food ingested.

The composition of normal feces is as definite as is sodium chloride. If a bit of feces is rubbed up with distilled water and filtered, practically all will pass through the filter; only the large unbroken particles, such as spinach tissues and stems, seeds, etc., remain in the filter. Under the ultra-miscoscope the filtrate is seen to be a perfect colloidal suspension, *viz.*, small rounded, rod-shaped particles, approximately 25% of which are colon bacilli, some motile, most of them dead; and approximately 75% cellulose. Normally, in the unfiltered specimen, an occasional meat fiber is seen, very rarely an unbroken vegetable cell. In brief, normal feces produced from a general mixed diet is a perfect colloid; the larger vegetable tissues, seeds, skins, etc., are simply incorporations which are imbedded in the fecal colloid, much as the housewife sometimes incorporates fruits in a gelatine dessert. It is only when such are present in abnormally large quantities that they have any significance. It is the homogeneous, colloidal mass which constitutes normal feces.

Clinically, all normal feces naturally divides itself into two main types: the constipated stool, small in quantity, dark in color, formed, inspissated, expelled with difficulty; and the "good drainage" stool, large in quantity, light brown in color, soft in consistency and easily expelled. In practice we of course, find varying mixtures of these two types, and the degree of drainage depends directly upon which type prevails. The only essential difference between the two types is in the contained water. The good drainage type contains approximately 70% water, while the constipated type contains but 30% water. The water in both instances is held in chemical combination with the colloidal particles; it is never normally present as free water.

Fecal colloids (as well as other colloids) take on water because of a peculiar property known as imbibition, *i.e.*, the power of taking on water without forming liquid solutions. The factors which control the quantity of water which will be taken on by a colloid are the pH of the medium in which a colloid is suspended, and the iso-electric point of the individual colloid. The greater the difference between the pH of the suspending medium and the iso-electric point of the colloid, the greater the intake of water of imbibition, and hence the more thorough the drainage.

If feces of any type is rubbed up with distilled water, it will be found to have an iso-electric point of approximately 4.5. If the pH of a good drainage stool is determined, it will be found in the neighborhood of 7.2. The good drainage type of stool therefore shows a difference between the iso-electric point and the pH of the specimen of approximately 3, on the acid side, which accounts for the intake of two-thirds more water of imbibition. On the other hand, the pH of the constipated type of stool will be found to approximate the iso-electric point. When the iso-electric point and the pH of a specimen are identical, imbibition does not take place, and it is this lack of water of imbibition which produces the hard, formed, constipated stool. In practice we meet with mixtures of these two types, the pH ranging all the way from 7.2 to 4.5 and the degree of drainage (or constipation) varying as the difference between the pH and the iso-electric point.

pH is a symbol which indicates the concentration of H ions or active acidity in a solution or colloidal suspension, while the iso-electric point is that pH at which colloidal particles are electrically neutral or inactive. The pH of feces is determined by rubbing up a weighed quantity of feces in distilled water and filtering. The pH of the filtrate is electrically determined.

The iso-electric point of feces is determined by making a suspension of feces in solutions of different known pH values. A small quantity of the different suspensions is placed in a concave slide and the positive and negative poles from a high voltage battery are dipped into the suspension. The procedure is carried out under the low power microscope. When the circuit is closed the fecal particles can be seen to rush across the field to the positive pole, indicating that fecal colloids carry a negative electrical charge. When the pH of the suspending medium and the iso-electric point of the colloid are identical, the particles do not migrate when the circuit is closed.

A determination of pH and the iso-electric point of feces requires delicate and expensive apparatus, which, for practical purposes, is unnecessary. Clinically, the degree of drainage and the type of feces can easily be determined by placing a weighed quantity of feces in a Petric dish and drying in the warm air incubator. A "good drainage" stool contains approximately 70% water, while the constipated stool contains approximately 30% water. The experienced clinician however, can tell at a glance the degree of drainage by noting the color, consistency and quantity of stool.

Inasmuch as the iso-electric point of all feces is approximately 4.5, the practical application of the above observation resolves itself into how to control the pH of the feces. Observation has taught us that this can be done by the administration of large quantities of starch — quantities in excess of the pancreatic threshold, so that all of the starch cannot be hydrolyzed during its passage through the upper bowel. If more starch is taken than can be hydrolyzed by the available amylase, the excess passes to the colon where it meets with bacteria of the acid forming series. As a result of the action of these bacteria upon the starch and sugar, lactic and other acids in large quantities are formed. It is these acids, arising from colon carbohydrates, which determined the pH of the feces.

Practically, normal drainage can be quickly established by having the patient include in the regular diet a large helping (the more the merrier!) of any starch. The stool produced in this manner (which we prefer to call the "good drainage" stool or carbohydrate stool) is large in quantity, light brown in color, soft in consistency, results in but one daily evacuation, can be recognized at a glance, and leaves the patient with a delightful sense of completeness and thoroughness.

It is of course, presumed that the patient has previously been examined so as to preclude all pathological conditions which interfere with or prevent normal drainage. Likewise, the doctor should himself "see" the stool. Patients have many peculiar ideas concerning bowel drainage. They should be informed that

good drainage depends, not upon the number of daily evacuations, but upon the thoroughness of drainage. Many patients will report failure because the bowels have moved but once in 24 hours, while they believe that two or more evacuations are necessary; or because the quantity, in their estimation, is not sufficient; or because the stool is not watery and expelled with explosive force as following a cathartic.

CONCLUSIONS

1. The mechanism of normal bowel drainage depends upon the maintenance of a difference, on the acid side, between the pH and the iso-electric point of the feces.

2. The pH of the feces, and hence normal drainage, can quickly be controlled by the administration of starch in excess of the pancreatic threshold.

The Elimination of Various Dyes from the Pavlov Pouch of Dogs

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THE elimination of dye stuffs by the gastric mucosa in various pathological conditions of the stomach and the study of this elimination experimentally in animals has received rather extensive recognition in recent years. However, valuable contributions such as those by Dawson and Ivy, Kobayashi and Henning are at such variance, that further studies on dye elimination were hardly possible without re-investigating at least those points of difference so strikingly obvious in the above reports. Furthermore any evaluation of dye elimination-studies makes it imperative that the differences already referred to either be verified or disproved.

Cellular and histo-chemical studies which may explain the mechanism of dye elimination as well as its possible clinical application depend upon end results with which all authors are in agreement. In the case of dye elimination there is definite disagreement. Hence, we have initiated the present experiments on dogs with Pavlov pouches using a large number of dyes, which were tested and studied after their injection in approximately 1% aqueous solution, intravenously, intramuscularly, and through other channels.

DYESTUFFS ELIMINATED BY THE STOMACH THROUGH PAVLOV POUCH FOLLOWING INTRAVENOUS INJECTION

1. NEUTRAL RED—*Azine—Weakly Basic*—(Indicator)—1%—40 c.cs.—toxic in that quantity. Does not stain the mms. (mucous membranes) of the stomach or tissues. Through in less than 5 minutes. Also comes through in 1 c.c. quantities used intravenously, and in 1% strength.

2. NEUTRAL VIOLET—*Azine—Weakly Basic*—1%—20 c.cs.—not toxic to the animal in the amount used. Amply through within 5 minutes. Mms. of the stomach stained pinkish-purple.

3. MAGDALA RED—*Azine—Basic*—1%—25 c.cs. Mms. stained slightly pink. Not toxic.

4. SAFRANIN O—*Azine—Basic*—1%—25 c.cs. slightly toxic in this amount. Mms. of the stomach stained pink. Comes through definitely, but not to a considerable extent. This is an etherized dog; stomach brought out and examined.

5. METHYLENE BLUE—*Thiazine—Basic*—1%—20 c.cs. Slightly toxic. Mms. of the stomach stained slightly blue. Comes through when 1 c.c. of a 1% solution is injected and not toxic.

6. METHYLENE BLUE (SPECIAL)—*Thiazine—Basic*—1%—25 c.cs. Mms. of the stomach not noticeably stained with this quantity. Tissues, tongue, etc., slightly stained. Not toxic. Comes through definitely although not as much as plain methylene blue.

7. METHYLENE BLUE MERCK—U.S.P.X.—*Thiazine—Basic*—1%—30 c.cs. Somewhat toxic. Mms. of stomach, and the tissues not noticeably stained with such an amount. Comes through better than methylene blue, special.

8. NEW METHYLENE BLUE N—*Thiazine—Basic*—1%—25 c.cs. Not toxic, mms. of the stomach not stained with this amount.

9. AZURE II—*Thiazine—Basic*—1%—40 c.cs. Mms. of stomach purple. Not toxic.

10. TOLUIDINE BLUE—*Thiazine—Basic*—1%—25 c.cs. Not toxic-stains the mms. of the stomach little if any.

11. THIONINE—*Thiazine—Strongly—Basic*—1%—40 c.cs. Mms. of the stomach stained bluish. Slightly toxic.

12. TETRAETHYL THIONINE—*Thiazine—Basic*—1%—40 c.cs. Mms. of the stomach stained slightly purple or bluish. (A sacrifice animal).

13. THIONINE BLUE—*Thiazine—Basic*—1%—25 c.cs. Not noticeably toxic. Mms. of stomach, and the tissues slightly stained.

14. BISMARCK BROWN—*Azo Group—Basic*—1%—40 c.cs. in a sacrificed animal. Amply through in 2 minutes. Mms. of the stomach stained brown.

15. CHRYSOIDIN—*Azo Group—Basic*—1%—20 c.cs. Through within 5 minutes. Mms. of pouch not noticeably stained.

16. ORANGE G—*Azo Group—Acid*—1%—40 c.cs. Mms. colored. Not toxic.

17. CONGO RED—*Azo Group—Acid*—(Indicator)—1%—40 c.cs. Pouch dog. Not toxic. Mms. of stomach

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stained red. Comes through definitely but not to a great extent.

18. TRYPAN RED—*Azo Group—Acid*—1%—20 c.cs. Through within 10 minutes, moderate amounts.

19. EOSIN—*Xanthene—Acid*—1%—40 c.cs. Mms. of the stomach colored pink. Slightly toxic in that amount.

20. MERCUROCHROME — *Xanthene — Acid* — Not toxic. 1%—20 c.cs. amply through in 2 minutes.

21. ERYTHROSINE—*Xanthene—Acid*—1%—25 c.cs. Mms. stained pink. Not toxic.

22. PHYLOXINE — *Xanthene — Acid* — 1%—25 c.cs. Mms. of stomach stained deeply pink. Not toxic.

23. ROSE BENGAL—*Xanthene—Acid*—1%—20 c.cs. Not toxic. Within 5 minutes through, although not to a considerable extent. Mms. of the stomach slightly pink.

24. IOZENE (Commercial germicide) — *Xanthene — Neutral?*—2%—solution of neutral sodium salt of monomercurotetra-iodo fluorescein. 10 c.cs. used. About 2¼ c.cs. per kilo. Not toxic and came through within 5 minutes. Mms. of the stomach and tissues slightly pink in color.

25. BASIC FUCHSIN—*Phenyl Methane—Basic*—1%—10 c.cs. Quite toxic. Stains mms. of the stomach deeply. Continued to be eliminated for 3 days. Seems to have temporarily caused impairment of secretory cells.

26. LITHIUM CARMINE—*Indigo Group—Acid*—1%—40 c.cs. Stains mms. a dark pink. Comes through slightly. Not toxic under ether.

27. ETHYL CAPRI BLUE NITRATE — *Oxazin — Basic*—1%—40 c.cs. (Cohen and Preisser). Mms. of the stomach stained blue. Not toxic.

28. MALLOPHENE (W. C. Holmes) (Gall Bladder Dye) (Mallinckrodt)—1%—20 c.cs. Through in less than 5 minutes. Mms. of the stomach not stained. Not toxic.

DYESTUFFS ELIMINATED BY THE STOMACH THROUGH THE PAVLOV POUCH FOLLOWING INTRAMUSCULAR INJECTION

1. NEUTRAL RED — *Azine — Basic* — 1% — 25 c.cs. Flank intramuscularly. Through amply within 5 minutes. Mms. of the pouch not stained. Slightly toxic.

2. NEUTRAL VIOLET—*Azine—Basic*—1%—20 c.cs. Through amply within 5 minutes.

3. METHYLENE BLUE—*Thiazine—Basic*—1%—25 c.cs. Intramuscularly in the flank. Through in small amounts after 30 minutes.

4. METHYLENE BLUE MERCK—U.S.P.X.—*Thiazine—Basic*—1%—20 c.cs. Through definitely in ample amounts within 5 minutes.

5. AZURE II—*Thiazine—Basic*—1%—20 c.cs. Small amounts through within 20 minutes.

6. TOLUIDINE BLUE — *Thiazine — Basic*—1%—30 c.cs. Intramuscularly in flank. Appeared within 15 minutes, definitely, but in small amounts.

7. NEW METHYLENE BLUE N—*Thiazine—Basic*—2%—25 c.cs. Intramuscularly. Mms. not stained with this amount. Definitely through within 30 minutes. Not toxic.

8. BISMARCK BROWN—*Azo Group—Basic*—1%—30 c.cs. Not toxic. Came through slightly after 5 minutes. Mms. of the stomach pouch not stained with such an amount.

9. CHRYSOIDIN—*Azo Group—Basic*—1%—20 c.cs. Definitely through within 20 minutes.

10. CONGO RED—*Azo Group—Acid*—1%—20 c.cs. Definitely through within 5 minutes.

11. EOSIN — *Xanthene — Acid*—1%—40 c.cs. Intramuscularly in a sacrificed animal. Through slightly after 15 minutes.

12. PHLOXINE — *Xanthene — Acid* — 1% — 40 c.cs. Flank intramuscularly into pouch dog. Through in small amounts after 25 minutes.

DYESTUFFS NOT ELIMINATED BY THE STOMACH THROUGH THE PAVLOV POUCH FOLLOWING INTRAMUSCULAR INJECTION

All of the dyestuffs that had been eliminated by the intravenous route were tried intramuscularly with the exception of Basic Fuchsin, which was too toxic, and Ethyl Capri Blue Nitrate and Mallophene, which could not be obtained.

1. MAGDALA RED—*Azine—Basic*—1%—20 c.cs. Not through.

2. SAFRANIN O—*Azine—Basic*—1%—20 c.cs. Not through.

3. THIONINE BLUE—*Thiazine—Basic*—2%—25 c.cs. Flank intramuscularly. Mms. of the stomach not stained with such an amount. Not through. Not toxic.

4. SPECIAL METHYLENE BLUE—*Thiazine—Basic*—1%—40 c.cs. Not through after 20 minutes.

5. THIONINE—*Thiazine—Basic*—1%—20 c.cs. Not through.

6. TETRAETHYL THIONINE—*Thiazine—Basic*—25 c.cs. of a 1% solution. Not through after 30 minutes.

7. ORANGE G—*Azo Group—Acid*—1%—40 c.cs. Into flank. Not through after 30 minutes.

8. TRYPAN RED—*Azo Group—Acid*—1%—20 c.cs. Not through.

9. MERCHROCHROME — *Xanthene — Acid*—1%—20 c.cs. Not through.

10. ERYTHROSINE—*Xanthene—Acid*—1%—40 c.cs. Intramuscularly into flanks. Not through. Not toxic. Mms. not stained.

11. ROSE BENGAL—*Xanthene—Acid*—1%—20 c.cs. Not through.

12. IOZENE—*Xanthene—Neutral?*—2%—5 c.cs. Not through.

13. LITHIUM CARMINE — *Indigo Group*—1%—20 c.cs. Not through.

DYESTUFFS NOT ELIMINATED BY THE STOMACH THROUGH THE PAVLOV POUCH FOLLOWING INTRAVENOUS INJECTION

1. TRYPAN BLUE—*Azo Group—Acid*—1%—25 c.cs.

2. JANUS GREEN—*Azo Group—Basic*—1%—25 c.cs. Toxic. Not through. Repeated on an etherized animal with similar results.

3. DIAZINE BLACK (Janus Black)—C.I. 134—*Azo Group—Basic*—1%—25 c.cs. Quite toxic. Mms. of the stomach pouch not noticeably stained. Repeated twice on sacrificed animals, 1%—40 c.cs. Did not come through.

4. METHYL RED—*Azo Group—Weakly Acid*—1%—20 c.cs. Not toxic, and mms. of the stomach and tissues not stained.

5. BORDEAUX RED — *Azo Group — Acid*—1%—20 c.cs. Not toxic.

6. METHYLENE VIOLET—*Thiazine—Feebly—Basic*—1%—25 c.cs.

7. GALLOCYANIN — *Oxazin — Basic* — 1%—20 c.cs. Not toxic.

8. BRILLIANT CRESYL BLUE—*Oxazin—Basic*—1%—25 c.cs. Stained mms. pouch slightly. (?)

9. CRESYLECHTVIOLET — *Oxazin—Basic*—1%—25 c.cs. Not toxic and mms. of stomach pouch not stained with this amount.

10. NIGROSIN—*Indulin*—No. 128. W. C. Holmes—(not a pure dye)—*Acid?*—1%—20 c.cs. Slightly toxic.

11. INDIGO CARMINE—Indigo Group of Natural Dyes—*Acid*—1%—25 c.cs.

12. HEMATOXYLIN—Indigo Group of Natural Dyes

Foot Notes:

1. It is apparent that many of the dyes which come through after intravenous injection do not do so after intramuscular injection.
2. Many of the dyes are indicators and therefore have both acid and alkaline ranges. This is important in all of these studies.
3. The factor of absorption of dyes by muscles must be taken into consideration.

—?—20 c.cs. of 1% solution. Not toxic. Mms. of stomach pouch not stained.

13. VICTORIA BLUE — *Diphenylnaphthylmethane—Basic*—1%—25 c.cs. mms. of pouch not stained. Not toxic.

14. GENTIAN VIOLET—*Triphenyl Methane—Basic*—1%—25 c.cs. Tissues not stained and not toxic.

15. ETHYLVIOLET—*Triphenyl Methane—Basic*—1%—25 c.cs. mms. not colored. Not toxic.

16. METHYL BLUE—*Triphenyl Methane—Acid*—1%—25 c.cs.

17. LIGHT GREEN—*Triphenyl Methane—Acid*—2%—25 c.cs. *Not toxic and does not come through. Stains* tongue but not much of stomach.

18. ANILINE BLUE—*Triphenyl Methane—Acid*—1%—25 c.cs. mms. of pouch not stained.

19. PYRROL BLUE—*Triphenyl Methane—Acid*—1%—25 c.cs.

20. BRILLIANT GREEN—*Triphenyl Methane—Basic*—1%—25 c.cs. Not toxic, and mms. of the pouch not stained.

21. AURAMINE—(W. C. Holmes) C.I. No. 655—*Diphenyl Methane—Basic*—1%—20 c.cs. Not toxic, and mms. of the stomach pouch and tissues not stained.

22. AURAMINE G—(W. C. Holmes) C.I. No. 656—*Diphenyl Methane—Basic*—1%—20 c.cs. Not toxic. Doesn't stain mms. of pouch or the tissues.

23. PYRONIN—*Xanthene—Basic*—1%—10 c.cs. Toxic, not through. Repeated using 40 c.cs. of 1% solution. Mms. of stomach and the tissues stained slightly on a sacrificed animal. Doesn't come through.

24. ERYTHROSINE (Al. Salt)—*Xanthene—Acid?*—1%—20 c.cs. Not toxic. Mms. not stained. Repeated, 1%—40 c.cs. Not through. Doesn't go into solution readily.

25. PHENOLSULPHONEPHTHALEIN—*Xanthene—Acid—(Indicator)*—1%—25 c.cs.

26. THYMOL BLUE — *Xanthene—Acid—(Indicator)*—1%—20 c.cs. into a pouch dog. *Mms. not colored. Dye* is toxic.

27. BROM CRESOL PURPLE—(Dibromcresolsulphonephthalein) — *Xanthene—Acid* — (Indicator)—1%—20 c.cs. Not toxic and mms. of the stomach pouch not stained.

28. BROM THYMOL BLUE—(Dibromthymolsulphonephthalein) — *Xanthene—Acid* — (Indicator)—1%—20 c.cs. Not toxic, and mms. of the stomach pouch not stained.

29. CRESOL RED — (O-Cresolsulphonephthalein) — *Xanthene—Acid*—(Indicator)—1%—20 c.cs. Did not stain mms. of the stomach pouch. Not toxic.

30. CHLOR PHENOL-RED — (Dichlorphenol)—*Xanthene—Acid*—(Indicator)—Did not stain mms. of the stomach pouch or the tissues. Not toxic.

31. FLUORESCEIN — *Xanthene—Acid*—1%—40 c.cs. on a sacrificed animal. Mms. of the stomach not stained with this dosage. It did not come through.

32. ISAMINE BLUE—*Oxazine—Basic*—1%—25 c.cs.

33. BERLIN BLUE—*La*—Unclassified—1%—25 c.cs. Tissues not stained.

34. PONTAMINE SKY BLUE—(513)—5 BX—Unclassified—1%—25 c.cs.

35. PONTAMINE SKY BLUE—AX—Unclassified—1%—25 c.cs.

36. PHENOLINDOPHENOL — Unclassified—1%—25 c.cs. Mms. of pouch not colored.

37. TOLULENE BLUE — *Thinzine — Basic*—1%—25 c.cs.

38. PONTAMINE BLACK—EX—Unclassified—2%—25 c.cs.

39. BENZAMINE RHEIN BLAU — (513) — *Azo — Basic*—1%—25 c.cs. Not toxic. Mms. of stomach pouch not noticeably stained.

40. NATIONAL ALKALI BLUE—2GP. CI-710—Unclassified—1%—25 c.cs. Not toxic and mms. of the stomach not stained.

41. NATIONAL ALKALI BLUE—4GP—Unclassified—1%—25 c.cs. Not toxic and mms. of stomach pouch not stained.

42. PONTAMINE GREEN — Unclassified — 1% — 25 c.cs. *Not toxic. Mms. of the stomach pouch not stained.*

43. JANUS BLUE—Unclassified—1%—25 c.cs. Mms. of stomach pouch not colored. Slightly toxic. Repeated with confirmation on sacrificed animals, 1%—40 c.cs.

44. LEUCOFAST GREEN—FCF—Unclassified—1%—25 c.cs. *Not toxic, did not stain mms. of stomach pouch* nor the tissues.

45. INDIGO MONOSULPHATE—Unclassified—1%—30 c.cs. Not toxic. Mms. of stomach pouch not stained.

46. INDIGO TETRASULFONATE — Unclassified—1%—30 c.cs. Mms. of stomach pouch not stained. Not toxic.

47. INDIGO DISULFONATE—Unclassified—1%—30 c.cs. Mms. of stomach pouch not stained. Tissues slightly stained.

48. DIANIL YELLOW—R—C.I. 649—W.C.H.—Unclassified—1%—25 c.cs. Rather toxic. Did not stain mms. *of stomach pouch.*

49. RHODULIN VIOLET—Unclassified—1%—15 c.cs. Quite toxic. Mms. of pouch and mouth pink—skin pink.

50. ALIZARIN SAPHVIOLET—1187—Unclassified—1%—20 c.cs. Toxic. Mms. of the stomach pouch not stained. Not toxic.

51. PONCEAU de XYLIDINE—Unclassified—1%—20 c.cs. Not toxic. Mms. of the stomach pouch not stained.

52. TARTRAZINE—(NAC)—W.C.H.—Unclassified—1%—20 c.cs. Not toxic and not through. Mms. of stomach *pouch not stained.*

53. PONTACYL LIGHT YELLOW—GG—Unclassified—1%—20 c.cs. Mms. of stomach pouch not stained. Not toxic.

54. DIANIL YELLOW—3G—C.I. 647—Unclassified—1%—20 c.cs. Mms. of the stomach pouch not stained. Tissues not stained. Not toxic.

DYESTUFFS NOT ELIMINATED BY THE STOMACH THROUGH THE PAVLOV POUCH FOLLOWING ADMINISTRATION VIA STOMACH TUBE

1. Aqueous solutions, 1 gram per hundred of distilled water, in amounts of 20 c.cs. were administered by stomach tube to pouch dogs. All of the dyes were used which had been shown to be eliminated after intravenous administration, with the exception of three dyes: Iozene, Basic Fuchsin and Ethyl Capri Blue Nitrate. Iozene and Ethyl Capri Nitrate could not be obtained in further supply and the basic fuchsin was felt to be too toxic for consideration. None of the dyes were eliminated in the pouch after an hour following the administration.

2. Neutral red and Neutral Violet were then separately tried by stomach tube in alcoholic solutions. One gram of each per 100 c.cs. of 70% alcohol were used. 20 c.cs. being the amount administered in each case. These dyes only were used, because it was felt that they were eliminated as quickly by the stomach as any of those tried intravenously and intramuscularly. An hour following administration, neither had appeared in the pouch.

Foot Note:

1. "Tissues stained or not stained" refers to complete autopsies which offered the opportunity of examining tissues (organs) in general.
2. If the contents of the Pavlov pouches had been dropped into basic solutions various dye colors may have appeared indicating secretion in a leuco form. In other cases treatment with a weakly acidifying solution may likewise have produced color indicating reduction of dye in muscle or other tissues.

DYESTUFFS COMING THROUGH GASTRIC MUCOSA (POUCH) AFTER RECTAL INSTILLATIONS

1. These results have not been satisfactory or constant up to the present time. 100 c.cs. of 1% neutral red instilled into rectum had come through the pouch after 12 hours. In some instances it appeared faintly 40 minutes after injection. This work is to be repeated.

DYESTUFFS COMING THROUGH GASTRIC MUCOSA (POUCH) AFTER INTRAPERITONEAL INJECTIONS

1. Those dyes which came through after intravenous and intramuscular injections were tried. These results have not been satisfactory up to the present time. The rectal and intraperitoneal routes are mentioned now because the former has not been tried heretofore while the latter has had only limited trial.

Basic fuchsin appeared to be a toxic dye and after its use there was no secretion of HCl. The animals in which this occurred and two other animals which had developed marked hypochlorhydrias approaching achylias were utilized for the injection of dyes which were known to be eliminated through the gastric mucosa. These experiments are to be repeated. However, it is interesting that methylene blue 1%, 25 c.cs., was excreted only in the smallest amount (there was a small amount of HCl). Toluidine blue, 1%, 25 c.cs., was injected into the oldest collie dog in which little HCl was excreted and no dye appeared.

REMARKS

1. 1% solutions (1 gram per 100 c.cs. of water) were employed. The dyes did not always dissolve 100% in the solvent; a moderate amount of heating was necessary in some cases. In those instances in which a solution of 1 gram to 100 c.cs. could not be approximated or in which solution was brought about with difficulty the dye was omitted or if used attention is called to the solubility difficulties.

2. In the future the authors recommend that instead of saying the mucousmembrane of the stomach pouch was or was not stained, a thing difficult to be certain of, it would be better to compare the heavy staining of the mucous membranes by such dyes as lithium carmine and phloxine with that of methylene blue, which stained them very little; such could be designated as (4 plus), vs. (plus—). To establish a standard intensity of staining requires further work and for that reason we are not prepared to offer this simplified scheme at present.

3. "Unclassified dyes" refers to those dyes for which reference works (Schultz, Conn) offer unsatisfactory information regarding their groups and acidity or basicity.

4. Disagreement with Kobayashi:—(our work is in disagreement with many previous investigators but since Kobayashi has made the more recent and extensive studies we call attention to these differences so that the importance of the present study is understood).

1. He reports Janus Black being eliminated by intravenous injection. This did not occur with us, even though it was 3 times repeated, using as high as 40 c.cs. of a 1 gram per 100 c.cs.
2. Several dyes, acid, which he reports as not being eliminated following intravenous injection were found by us to be eliminated quite definitely, namely the following:
   1. Congo Red
   2. Eosin
   3. Erythrosine
   4. Lithium Carmine
   5. Phloxine
   6. Trypan Red (and among the basic dyes)
   7. Fuchsin

5. Basic dyes do seem to be the ones most suited for elimination, particularly is this so in the intramuscular injections, these being predominantly the basic dyes, and the dyes most quickly and abundantly eliminated. Neutral Red, Neutral Violet and Methylene Blue are basic dyes. However, the degree of basicity is not proportional to elimination as is shown by Thionine (a strongly basic dye), neutral red and neutral violet (weakly basic) and the other basic dyes.

For the purpose of clarity the following table of Conn showing the grouping of dyes is appended.

Dyes of the Nitro, Azo and Oxyquinone Groups:

1. The Nitro Group
   - Picric Acid
   - Martius Yellow
   - Aurantia
2. The Azo Group
   - Orange G
   - Bordeaux Red
   - Janus Green B
   - Fast Yellow
   - Methyl Orange
   - Orange IV
   - Orange I
   - Narcein
   - Amaranth
   - Sudan III
   - Sudan IV
   - Biebrich Scarlet, Water Soluble
   - Bismarck Brown Y
   - Congo Red
   - Trypan Red
   - Benzopurpin 4B
   - Trypan Blue
   - Chrysoidin R
   - Chrysoidin Y
   - Others
3. Oxyquinone Group
   - Alizarin
   - Alizarin Red S
   - Purpurin

The Quinone-Imide Dyes

1. The Indamins
   - Toluylene Blue
2. The Thiazins
   - Thionin
   - Methylene Blue
   - Methylene Azur
   - Methylene Violet
   - Methylene Green
   - Toluidine Blue O
3. The Oxazins
   - Brilliant Cresyl Blue
   - Nile Blue Sulphate
   - Cresyl Violet
4. The Azins
   a. Amido-Azins or Eurhodins
      - Neutral Red
      - Neutral Violet

b. *Safranins*
Safranin O
Amethyst Violet
Magdala Red
c. The Indulins
Nigrosin, Water Soluble

The Phenyl Methane Dyes
1. Di-Phenyl Methane Derivatives
2. Tri-Phenyl Methane Derivatives
a. Di-Amino Tri-Phenyl Methanes
Malachite Green
Brilliant Green
Light Green SF, Yellowish
b. Tri-Amino Tri-Phenyl Methanes (Rosanilins)
Parafuchsin
Rosanilin
Basic Fuchsin
New Fuchsin
Acid Fuchsin
Hoffman Violet
Methyl Violet
Crystal Violet
Gentian Violet
Methyl Green
Iodine Green
Spirit Blue
Methyl Blue
Amilin Blue
Others

The Xanthene Dyes
1. The Pyronins
Pyronin G
Pyronin B
2. The Rhodamines
Rhodamine B
3. Fluorane Derivatives
Fluorescein (Uranin)
Eosin, Y (i.e. Yellowish)
Methyl eosin
Ethyl eosin
Eosin, Bluish
Erythrosin, Bluish
Phloxine
Rose Bengal
4. Phenolphthalein and the Sulphonphthaleins
Phenolsulphonphthalein (phenol red)
Brom Cresol Purple
Thymol Blue
Others

The Natural Dyes
The Indigo Group
Indigo (Blue)
Indigo Carmin
Litmus
Haematoxylin
Others

Classification of important biological dyes based upon chromophores (Conn). (They can be further grouped into acid and basic chromophores).
1. The nitro dyes
e.g. picric acid
2. The Azo Group
e.g. methyl orange, Bismark brown, orange G, Congo red, Sudan III and Sudan IV
3. The Oxyquinone Group
e.g. alizarin
4. The quinine-imide group, including
a. Indamins
b. Thiazins; e.g., thionin, toluidine blue, methylene blue
c. Oxazins; e.g., brilliant cresyl blue, Nile blue
d. Azins, including
(i) Amido-azins; e.g., neutral red
(ii) Safranins; e.g., safranin O, magdala red
(iii) Indulins; e.g., nigrosin
5. The phenyl-methane dyes, including
a. Diphenyl-methanes, e.g., auramin
b. Diamino tri-phenyl methanes; e.g., malachite green, brilliant green, light green
c. Triamino tri-phenyl methanes; e.g., basic fuchsin, acid fuchsin, methyl violet, gentian violet, methyl green, anilin blue
d. Hydroxy tri-phenyl methanes (Rosolic acids); e.g., aurin, corallin red
6. The *Xanthene dyes, including*
a. Pyronins; e.g., pyronin G and B
b. Rhodamines; e.g., Rhodamine B
c. Fluorane derivatives; e.g., eosins, erythrosin, rose bengal
d. Phenolphthalein and the Sulphonephthaleins

DISCUSSION

No attempt will be made at present to review the literature on the subject of dyes. It is voluminous and the reviews are many. Only a few of the more recent contributions will be discussed since they are necessary for the sequential development of the problem at hand.

After the work of Fuld and Finkelstein, Hirabayashi thought it of interest to observe the excretion of neutral red under various produced pathological conditions. In normal stomachs he observed, through gastric fistulas, the appearance of neutral red after the administration of an Ewald meal, calcium carbonate, histamine, pilocarpine and alcohol. He concluded that the speed with which neutral red appeared depended upon the intensity of secretion of the secretory glands. He now washed the stomach with ½% silver nitrate solution and found that after observations extending over 2 hours no dyestuffs appeared in the stomach though the HCl secretion was persistent. After 48 hours the stomach again secreted normally following histamin and dye injection. From these and similar experiments it appeared to Hirabayashi that a local damage to the gastric mucosa diminishes the intensity of secretion and leads to a reduction in dye excretion over that shown for the normal stomach. The stimulation with silver serves also to show that the glands were not able to excrete dye but that the secretion of HCl was not interrupted. It is therefore possible, Hirabayashi concludes, that the dye is excreted through the pepsin glands. We repeated this experiment and are in disagreement as shown by the following data.

ELIMINATION OF DYESTUFF FOLLOWING INTRAVENOUS INJECTION AFTER THE STOMACH HAD BEEN TREATED WITH SILVER NITRATE SOLUTION

Ninety c.cs. of ½% solution of silver nitrate was administered to a pouch dog by stomach tube, and the pouch was washed with ½% silver nitrate solution. Ten minutes later 20 c.cs. of a 1% solution, aqueous, of neutral red was injected intravenously. Within 2 minutes the dye appeared from the pouch and in the stomach as amply as had been found previously. The same results were obtained with the stomachs of white rats.

Our results are entirely different from those of Hirabayashi, and they corroborate other conclusions

which we have been able to reach regarding the mechanism of neutral red excretion. This mechanism is of fundamental importance in the study of certain diseases as we hope to point out in future communications.

Dawson and Ivy studied the elimination of dyes by the gastric mucosa. They used dogs with an isolated fundic pouch (Pavlov Pouch) and dogs with an isolated pyloric pouch, the latter animals being used to ascertain if certain dyes were eliminated by the mucus cells. Of thirty-three dyes studied, thirteen were eliminated in the gastric juice. However, we were unable to corroborate these results in their entirety. Dawson and Ivy report a relationship between the amount of dye eliminated and the rate of secretion, i.e., the more gastric juice, the more dye eliminated. On the other hand, they report the elimination of neutral red through the pyloric pouch when the mucosa of the pouch was activated with gastric juice. It seems hardly possible that this was actual elimination, because we have been able to demonstrate a selective secretory mechanism for neutral red. Dawson and Ivy could not predict the effect of a dye from a study of its chemical constitution but they mention selective secretion as an obvious factor that must be considered in dye elimination, that is, some dyes may possibly be eliminated through the parietal cells, others, through the chief cells or mucus cells. Several dyes, of which neutral red is the best example they write, can be detected by microscopic examination to be passing out through the parietal cells as the secretion in the canaliculi is rendered conspicous by the dye. It would be difficult to correlate this finding with the elimination of neutral red through the pyloric pouch since the pylorus (unless the pouch included some oxyntic cells) contains no parietal cells. Dawson and Ivy believe that under certain conditions neutral red though most readily eliminated by the parietal cells, can be eliminated by the mucous cells of the stomach. They conclude finally that the parietal cells are the cells chiefly concerned in the elimination of dyes by the gastric mucosa and whether or not a dye is eliminated by these cells depends on some unknown as yet physical rather than chemical property of the dye as there is no chemical property characteristic of the dyes that are eliminated. Furthermore it seemed to them that the problem of dye elimination by the gastric glands has a greater scientific import than practical value. By comparing our Table with their's the importance of repeating these dye elimination tests becomes apparent. For example in our tests neutral violet came through amply, in the tests of Dawson and Ivy the result was negative. Moreover, the extensive reports of Kobayashi are not entirely corroborated by our investigations and attention has been directed to some of the differences.

Kobayashi has studied the absorption, secretion and excretion of dyes perhaps more extensively than any other recent investigator. He cannot agree with the conclusion of other investigators that the mechanism of the elimination of dyestuffs into the stomach could be explained simply by diffusion or that it depended on the gastric secretory function. He also disagrees with Hirabayashi's conclusions for he believes it must be the gastric glands and especially the parietal cells that secrete the dyestuffs. Matsuo as well as Glaessner and Wittgenstein, the latter in histological studies of neutral red elimination, support Kobayashi in this latter opinion. Kobayashi's experiments were very well controlled and minutely observed and he was able to correlate the concentration of eliminated dyes, hydrochloric acid and the pepsin. His experiments also confirmed the lack of relationship between the diffusibility of dyestuffs and their intensity of elimination; the lipoid solubility of dyestuffs did not explain their elimination into the stomach. Acid dyestuffs in general, were found not to be eliminated into the stomach even when soluble in lipoids. Our work would not support this observation although we too, found that basic dyes were predominant among those passing through the gastric mucosa. Kobayashi investigated 65 acid dyes; all of them had different properties physico-chemically or biologically, that is, in chemical construction, in diffusibility, in solubility in lipoids, or in vital staining, but none of them were perceived in the gastric juice.

Kobayashi concludes that the dyestuffs which are eliminated into the stomach are chlorides of dye bases and have amidogroups or their alkylsubstitutes in their auxochrome. They belong to the azo, azine, oxazine, thiazine or acridine group and their chromogens have all —N= in their chromophores and greatly resemble the fundamental unit of protein. They have some diffusibility and all have a positive charge. Kobayashi points out the resemblance in construction between these chromogens and the fundamental unit of protein and consequently he continues, "the dye bases of these dyes may be considered to have a construction similar to protein itself in some points." He suggests that this may be the reason why only the dyes of these groups can be eliminated into the stomach. Finally the elimination of dyestuffs is explained by a mechanism similar to the secretion of hydrochloric acid; he shows that his explanation harmonizes very well with the fact that when the parietal cells secrets HCl in a high concentration, they secrete dyestuffs in a relatively large quantity. The concentration of pepsin did not run parallel to that of the dyestuffs as exactly as the acidity. When the concentration of hydrochloric acid in the gastric juice is increased by a pilocarpine injection, the concentration of dyestuffs eliminated into the stomach is also increased and when the former is decreased by atropin. the latter is also decreased. Also with patients, Kobayashi found the curve of concentration of neutral red eliminated into the stomach after its administration into the blood circulation generally to run parallel with that of hydrochloric acid in the gastric juice. The work is indeed convincing and we have been able to corroborate it except that in our dye tests several acid dyes were found to be eliminated through the gastric mucosa. This finding necessitates another explanation of the mechanism of dye elimination than that offered by Kobayashi. The important fact however is the verification of the physiological mechanism of dye elimination. Knowing this, it becomes applicable for clinical use especially as a diagnostic measure to say nothing of the interpretation of pathological change which it allows. Further development of this topic will come later.

In 1932, Henning reported his work on the excretion of dyestuffs through the gastric mucosa of frogs. This work was based on some earlier clinical work which Henning, Jurgens and Orstein did in collaboration in 1931. The experimental arrangement was unique in that frogs, the gastric mucosae of which are almost

completely transparent were used while under the quieting influence of urethan. The stomach of the narcotized frog (urethan) was opened at the greater curvature and by an appropriate technique the excretion of a given dyestuff from the stomach could be followed visually in all its phases. The results obtained are remarkable when compared with Dawson and Ivy's and Kobayashi's for after testing a long series of dyestuffs it was shown that only acid dyestuffs are excreted into the stomach, provided they are in sufficiently fine dispersion; basic dyestuffs are not so excreted. As an example, the microscopical study of neutral-red excretion shows that the indicator in red color first appears on the surface of the mucosa, while it passes through the mucosa as neutral yellow. Accordingly, the gastric hydrochloric acid is first formed on the covering epithelium. The dyestuff excretion Henning reports "is a function of the fundus glands: the antrum glands do not participate." Dawson and Ivy reported neutral-red excretion through a pyloric pouch in the dog. The excretory function of the gastric mucosa, Henning concludes, is connected with the secretory function. It can be elicited in secretory rest by means of secretory stimulants (histamin). In other words, the excretory function of the gastric mucosa is closely related to the secretory function; it stops on secretory rest and can be elicited through histamin. Uranin (fluorescein), eosin, erythrosin (all acid xanthene dyes) neutral red (weakly basic azin), Congo red (acid azo) magdala red (basic azin), trypan blue (acid azo) and methylene blue (basic thiazin) were a few of the dyes which came through the gastric mucosa. It will at once be seen that 3 of these dyes are basic which makes it difficult to understand the conclusion that only acid dyes are eliminated, except that Henning refers to neutral red as an indicator dye and therefore acid as well as basic. Furthermore, except for Henning there is general agreement that trypan blue is not eliminated through the gastric mucosa. We found that it was taken up by the phagocytic cells but was *not* in the glandular cells. Moreover, in our work trypan blue was injected intravenously into a rabbit and followed by neutral red; the latter appeared through the gastric mucosa but the trypan blue did not. Henning finds that trypaflavin is taken up by entirely different cells than uranin. The dyes mentioned above all electively begin to stain the capillary walls, the submucous connective tissue and the glandular cells. Henning recalls the extensive experimentation on albino rabbits of F. P. Fisher who showed that the different behavior of the dyestuffs is determined by their colloid constitution and that the fate of dyestuffs which have been introduced into the blood current, is governed by the degree of dispersion, the electric charge and surface tension phenomena.

SUMMARY

In order to furnish a working basis for further investigations it has become essential to repeat the study of dye elimination through the gastric mucosa. Without reviewing the voluminous literature, three representative and rather recent papers are examined to show how extremely varied the results have been. Often the differences are so extreme that reasons are sought to explain them either in the type of experimental animal, the method of experimentation or the interpretation of results. It becomes apparent that our interpretations explain some of the incongruities but there still remains a fundamental difference in results. All are agreed that it is the fundus mucosa which eliminates those dyes which are excreted. We too, have reached this conclusion but furthermore, we have found that both acid and basic dyes are eliminated (more of the latter) which differs from the results obtained by the other investigators. Many dyes may be both acid and basic. In fact, the acid or basic reaction of many dyes depends on the nature of the subgroups which confer water solubility upon the molecule. Our work corroborates parts of each of the other investigators but not enough to substantiate any of their explanations of the mechanism of dye elimination nor the reasons for selective elimination. It would seem that size of dye particles apparently plays little role since it has been shown by the ultrafiltration experiments of Allisbaugh and Hyde that methylene blue, a dye readily eliminated, is considerally larger in particulate size than a dye definitely withheld. Careful study of the present investigation leads us to the conclusion that it represents a reliable basis for the studies which we are pursuing but it does not allow us, as yet, to explain either mechanically, physiologically or chemically dye elimination by the mucosa. This we hope to do in a future communication.

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SECTION III—*Nutrition*

On the Probable Frequency of Allergic Shock

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A REVIEW of the literature reveals surprisingly few accounts of clinical anaphylactic shock. In spite of what we consider the relative frequency of these events they have received comparatively little attention in recorded reports.

Lamson in a meticulous review of the literature from 1895 to 1923 reported "41 cases in which death may have been due, directly or indirectly, to protein injections." These fatalities, in tabulation, are as follows: from diphtheria antitoxin, 31; anti-tuberculosis serum, 1; normal horse serum, 2; anti-streptococcus serum, 1; tetanus antitoxin, 2; antipneumococcus serum, 1; proprietary biologic product for muscular rheumatism, 1; liquid glue, 1; and probably ovomucoid, 1. In this series he included five personal observations; four from diphtheria antitoxin and the fifth due probably to ovomucoid. In the same series Lamson reported 21 additional cases "in which information was lacking, or in which death seemed due to primary disease or some other cause not associated with injected substances." These included: from diphtheria antitoxin, 13; anti-meningococcus serum, 4; anti-staphylococcus serum, 1; pneumococcus antibody solution, 2, and human blood transfusion, 1. Since Lamson's report there have appeared several references to shock from serum and other proteins, and non-nitrogenous factors as well, but their sparseness is noteworthy in view of the fact that administration of protein and non-protein agents for diagnosis, prophylaxis and treatment has been on the increase.

We have reviewed the literature from the period of Lamson's report up to and including 1935 as recorded in Table I. These cases include reactions not only to serum and other proteins, but to non-nitrogenous substances as well. They are classified as to number of cases, method of administration of shocking agents, and outcome. Of the 68 cases those associated with serum administration are in the majority, numbering 35. These include hemoplastic preparations, anti-meningococcus serum, diphtheria antitoxin, anti-streptococcus, plain horse and anti-pneumococcus sera. Other causes of shock were bee sting (4 cases); aspirin (3 cases); wasp sting (2); egg white (2); milk (2); rye (1); grass pollen extract (1); glue (1); sodium iodid (1); bismuth tartrate (1); rabbit hair inhaled (1); green pea (1); quinine hydrochloride (1); walnut (1); buckwheat (1); feather extract (1); commercial cold vaccine (1); ovomucoid (1); blood transfusion (2); puncture of hydatid cyst (4); and gum acacia (1).

The methods of administration or exposure were varied. The *intramuscular* route included ten serums and one milk; *intravenous*, two serums, 1 milk, 1 sodium iodid, 1 bismuth tartrate; *oral*, 1 milk, 1 green peas, 3 aspirin; *inhalation*, 1 rabbit hair; *intracutaneous*, 1 serum, 1 glue, 2 egg white, 1 buckwheat, 1 ovomucoid; *subcutaneous*, 12 serum, 1 morphine, 1 Bermuda grass pollen, 1 commercial cold vaccine; *scratch*, 1 walnut, 1 rye; *transfusion*, 2, and *"unknown,"* 20.

The "outcomes" are classified as fatal, recovered and unknown.

Not all of the cases included can properly be described as clean cut. Severe reactions have been observed following blood transfusions, even though apparently satisfactory matching had been accomplished beforehand. Bender and Traum have described anaphylaxis following blood transfusion which they attribute to serum idiosyncrasy. Waldbott in describing a case which reacted to feather extract, states that the reaction was not typical or similar to that following injection of pollen extract. The feather extract, which he believes to have been given intravenously by accident, gave rise to a severe migrainous headache with vomiting and cloudy spots before the right eye, manifestations which the patient had frequently experienced before. The same type of reaction occurred in his case who was given therapeutic extract for eczema, resulting in a severe generalized urticaria.

It is interesting to note that Lamson found in his survey (up to 1924) only two reported cases of anaphylaxis from substances other than serum. In 1922, Cooke described a case of shock occurring from liquid glue applied as a diagnostic skin test. The other case was a personal observation by Lamson of shock from diagnostic skin test which he thought to be due to ovomucoid. In the surveys represented herein there are only 35 cases of serum shock, representing 52 per

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cent of the entire series. Of the remaining cases 27 or 38 per cent of the total were shocked from protein other than serum, while 7 or 10 per cent of the total were shocked from non-protein substances.

Although the literature as briefly reviewed above would indicate that severe allergic shock and death are extremely infrequent, we have felt that in view of the widespread use of allergenic materials the possibility existed that the phenomenon was much more frequent than appeared. This would be especially likely to be the case in view of the natural disinclination that many would have towards reporting unfortunate experiences.

When therefore, in 1935, one of us was demonstrating an exhibit on allergic shock at the meeting of The American Medical Association, an effort was made to interview as many as possible of the doctors who stopped at the booth, concerning any experiences that they had had or had known of among their colleagues. While this was purely a random selection the possibility must be acknowledged that a physician who had had an unfortunate experience of this type would be more likely to stop at the booth.

A total of 50 physicians was interviewed, 25 of whom had either personally observed severe shock or knew of such cases among colleagues in their home towns. For obvious reasons names and addresses were not asked but as much information as could be was obtained from the informants.

Two types of case were excluded: those that had been reported in the literature, and those of what we term "severe allergic reaction." A severe case of urticaria or even asthma following the administration of an overdose of pollen extract is a severe allergic reaction but is not shock. We feel that allergic shock is a much more explosive affair, developing with extreme rapidity, once it has started, and due in all probability to a quite generalized tissue edema, including interstitial edema of the lungs, and due to almost universal increase in capillary permeability. The mechanism is probably quite similar to that responsible for urticaria and differs principally in its extremely widespread distribution. It should be borne in mind that the capillaries of the muscles alone in the average man have a total area of approximately 6,300 square meters, or more than 3,000 times the area of the entire body surface. It has been stated that in the absence of restraining forces, the entire plasma volume could pass from the capillaries into the body tissues within ten seconds. (Editorial: "Capillary Pressure and Capillary Permeability." *J. A. M. A.*, 103:920, 1934). With this in mind persons were asked particularly regarding the presence or absence of urticaria and asthma. While some of those interviewed were uncertain the number who stated definitely that the symptoms were not inaugurated with urticaria or asthma was surprisingly large. This will be brought out below.

Some reactions, notably those to drugs are probably not allergic but are included for general interest and because they were mentioned.

In an effort to provide some sort of a check on these random interrogations and to see whether sampling of a slightly different type of population would give materially different frequencies, one of us repeated the procedure in the autumn of 1935 at the meeting of The Medical Society of Virginia. Twenty-five physicians were interrogated, of whom 14 described cases of shock.

The information obtained is briefly summarized in the accompanying table.

Some of the more interesting cases were described as follows:

SERUMS AND ANTITOXINS

There was one death from plain horse serum given subcutaneously for postpartum hemorrhage.

A boy had had tetanus antitoxin two years previously. On the second injection of antitoxin he developed typical anaphylactic shock.

A person was given tetanus antitoxin prophylactically into the abdominal muscles. One minute later he developed angioneurotic edema of the face and wheezing. He could not breathe. He was given adrenalin with relief. Six days later he had regular serum sickness. Three years previously he had had toxin-antitoxin. During childhood he had facial eczema.

The reaction in another case followed intracutaneous testing with 0.1 c.c. of tetanus antitoxin diluted 10 times. The reaction commenced before the dector could get the syringe cleaned. It consisted of nausea, vomiting, sneezing, asthma and urticaria. Treatment with adrenalin resulted in prompt relief within half an hour.

A cook had diphtheria. There were twin daughters in the home. One of them had been subject to hives. The father, a physician, gave the second daughter, not subject to hives, 1000 units of diphtheria antitoxin prophylactically. She was dead in five minutes.

A child had diphtheria and the physician decided to immunize the entire family. The father dropped dead.

A colored boy with diphtheria received antitoxin. There had been no previous serum administration. He went into collapse within three minutes. There was no urticaria. He received adrenalin with subsequent recovery. Four days later he had serum sickness.

A patient with scarlet fever was given erysipelas streptococcus antitoxin. The intracutaneous test had been negative. He received 2 c.c. intravenously over a period of ten minutes. "One hour later" he had a severe reaction with cyanosis, respiration 45, pulse thready, blood pressure 120, going later to 70. Relief was obtained after about 45 minutes with adrenalin. There was no allergic history and no previous serum injection.

Scarlet fever antitoxin was given to a patient who had previously received serum of some kind. Within five minutes he was in collapse and pulseless. He was given adrenalin and recovered from the acute response but died later from the scarlet fever.

A patient with pneumonia was given anti-pneumococcus serum which was very promptly followed by coma. The pulse was very slow. The physician thinks that the condition may have been psychic.

POLLEN EXTRACTS

A physician had been giving himself his own shots of prophylactic ragweed pollen extract. He was toward the end of the series. He had a typical shock type of reaction without urticaria, hay fever or asthma. This began within five minutes after the injection. The physician stated that if he had waited five minutes longer he could not have left his chair to get the adrenalin. Prompt relief was obtained in ten or fifteen minutes following adrenalin injection. He has not taken any treatment since. He had taken courses of treatment for the five previous years, but had never obtained extremely good results.

A traveling man had been in the habit of rushing into various doctors' offices, wherever he happened to be, getting the doctor to give him a shot of pollen extract and then promptly rushing back to his car and driving on. One day he followed this customary procedure in a small West Virginia town. After he was back on the road he

went into shock. He did at last manage to get to a farm house from where a physician was called.

A patient received his fifth injection of ragweed extract. He promptly went into coma and respiration ceased. He was pulseless. The patient eventually recovered. The doctor feels confident that this was not psychic.

A patient was being desensitized with ragweed extract. Injections were given every third day. Within one minute after the fourteenth treatment the patient collapsed, with loss of sphincter control and coma. During recovery he commenced to have hives. During shock the pulse and respiration were slow. Treatment was given with adrenalin, with recovery in 30 to 60 minutes. The next day he was entirely himself again.

A patient had been receiving perennial ragweed treatment with two injections monthly. He missed one dose and at the end of thirty days came in for treatment. He was given the usual 0.1 c.c. of 1 33 concentration. He walked to his office five minutes away and then promptly went into coma. He had enough intelligence to take an ephedrin capsule before losing consciousness and his assistant applied a tourniquet. One hour later he was entirely all right. No adrenalin was administered.

A patient had been receiving injections of ragweed oil for ragweed dermatitis. He went into shock within two minutes which was followed by severe abdominal pain and extreme headache whenever he would raise his head, all of which lasted about five hours. He did not lose consciousness. There was little urticaria and no asthma. Following this his ragweed dermatitis was entirely cured for several weeks.

A patient was being desensitized with timothy extract, had left the doctor's office and was working beneath his automobile. He had typical anaphylactic shock and had great difficulty in getting out from under the car to procure aid. This was an early small dose of timothy extract.

A woman, aged 60, had received preseasonal and coseasonal pollen treatment for six or seven years without benefit. After an interval of several years without treatment she saw a new doctor who gave her preseasonal and coseasonal treatment with very satisfactory results. A year later, at the onset of symptoms, she received 0.1 c.c. of 1 10,000 mixed ragweed. This was from the same bottle that had been used the previous year. Within thirty seconds she was comatose and in convulsions. The coma lasted about five minutes. This was followed by slight urticaria and pronounced asthma. She remained seriously ill for an hour and a half. Following this one episode she had no further treatment for the season and had no hay fever. One year later, during the season she had ten or eleven coseasonal injections with good results.

A case of anaphylactic shock occurred during desensitization therapy with extract of rose pollen. This was early in the treatment, the third injection.

ALLERGY TEST MATERIALS

A negro orderly in a hospital who received a scratch test with 3 per cent concentration of ragweed extract collapsed and went into coma within three minutes. Blood pressure was 85. Pulse was rapid and thready. Respiration was normal. He remained unconscious for half or three-quarters of an hour. He was treated with adrenalin. Late during the period of collapse, before complete recovery, he developed urticaria. There were no nasal or bronchial symptoms. During the preceeding three years he had had coseasonal treatment with perfect results, receiving only three or four injections each season.

The wife of a farmer inhaled large quantities of smoke when the barn burned down. Thereafter she would always have attacks of asthma when wood fires were lighted in the fire place. She was tested with extract of wood smoke. Extract of wood smoke is prepared commercially for the curing of ham. Following the scratch test she promptly went into collapse but recovered.

In another case scratch test with streptococcus vaccine had been negative. The same material was then tried intracutaneously. A systemic reaction followed within sixty seconds. This was accompanied by asthma and urticaria. It lasted for two hours and required a total of 3 c.c. of adrenalin for relief.

An intracutaneous test with 0.05 c.c. of concentrated horse serum, preliminary to the administration of antitoxin resulted in death within five minutes. There had been no previous scratch test.

An intracutaneous test with 1/10,000 dilution of annual sage extract promptly resulted in a very strong intracutaneous reaction with generalized itching, generalized urticaria, brassy cough, asthma, blood in the sputum and vomiting. Adrenalin had to be administered every 50 minutes throughout a period of twenty-four hours. The reaction was followed by an anuria, after which so much albumin appeared in the urine as to produce a solid clot in the test tube. The patient received a total of 60 injections of adrenalin. As the physician expressed it "all of her mucous membrane were involved including the kidneys."

FOODS

A doctor described two instances of collapse in infants when first given cow's milk. In each case the child vomited, became very pale and the family thought he was dead. One of these children had no hives, the other had hives during recovery only.

A case of anaphylactic shock was described following the eating of egg. This boy had been to a Thanksgiving dinner and ate some mashed potatoes to which egg had been added. The child went into coma, two or three doctors were called and three hours elapsed before recovery.

A man sensitive to ragweed promptly went into shock without asthma or urticaria following the eating of wild honey. The physician is of the opinion that it was due to the ragweed pollen in the honey. It is well known that bees deposit quantities of pollen in honey.

After the eating of a single cherry a woman promptly experienced angioneurotic edema of the mouth and edema of the larynx. She had had a similar experience from a blackberry pie at another time. Adrenalin gave relief on both occasions. This was early in the days of adrenalin therapy and the physician gave her 2 minims of 1/1000 intravenously. Thereupon he thought that she died. "She stiffened out, took a long breath, and was all right."

DRUGS

A man, aged 55, knew that even the touching of his lips with aspirin would result in cyanosis and asthma within thirty seconds. On an occasion he had a headache and a friend gave him a powder which, unknown to him, contained aspirin. This resulted in a severe reaction which lasted five hours and required several doses of adrenalin.

Powdered aspirin was applied to the throat following tonsillectomy, in a man of 35 years. It promptly produced intense dyspnoea and cyanosis. The patient cried out, "My God, what did they give me?" He had had similar experiences previously from aspirin. Adrenalin administration was followed by recovery.

A five grain aspirin tablet caused prompt shock, collapse and cyanosis. There was no urticaria. There was some subsequent pulmonary edema but no asthma. Adrenalin administration resulted in recovery in a few minutes. The patient had had aspirin before but never with severe symptoms.

An asthmatic patient with low blood calcium was receiving calcium gluconate intravenously. At about the time when he commenced experiencing heat in his mouth he broke out into a cold sweat and according to the doctor went into typical shock. Treatment was with adrenalin and recovery was slow.

A colored woman received an injection of neoarsphenamin. She had had several previously. To this one she

TABLE I

Method of Administration

Substance	Number of Cases	Intram.	Intrav.	Oral	Inhalation	Endermal	Subcut.	Scratch	Transf.	Unknown	Outcome Fatal	Outcome Recov.	Outcome Unknown
Serum	35	10	2			1	12			10	11	13	11
Morphine	1						1						1
Bee sting	4											4	
Milk	2	1		1							1	1	
Pollen Berumda grass	1						1				1		
Glue	1					1					1		
Egg white	2					2					2		
Sod. iodid	1		1									1	
Bismuth tartrate	1		1								1		
Rabbit hair	1				1							1	
Pea green	1			1							1		
Quinidine hydrochloride	1		1									1	
Walnut	1							1				1	
Buckwheat	1					1							
Rye	1							1					
Feather extr.	1		1									1	
Cold vaccine	1						1					1	
Wasp sting	2												
Blood	2								2				2
Ovomucoid	1					1					1		
Aspirin	3			3							3		
Hydatid cyst punctured	1												
Gum acacia	1		1									1	

reacted with vomiting and collapse. Adrenalin was given with recovery.

A death was reported five minutes after an intravenous injection of neoarsphenamin.

BIOLOGICALS

A woman was sensitive to veal, ragweed, June grass and orchard grass. For an attack of menorrhagia she was given Antitutrin S. At once she developed urticaria, became cyanosed and went into shock. The doctor expressed it that she puffed up like a pouter pigeon. There was coughing and vomiting. Treatment was administered with adrenalin and it required four or five hours before recovery. The urticaria persisted for four or five days. She had been tested with veal some time previously and had reacted positively thereto by skin test. She had avoided veal since childhood. This patient was subject to attacks of petit mal.

Brook's hemoprotein has been used as foreign protein therapy for sinusitis. In one case its administration was followed promptly by severe constriction of the bronchial muscles, itching of the mouth and scrotum. Reaction was almost immediate. Adrenalin was given, with prompt relief. There had been several similar injections previously without untoward effect.

Early in the course of intramuscular liver therapy a first intramuscular injection was given. The patient had previously taken liver extract by mouth. Within three minutes she was pulseless and syanotic. There was no urticaria, hives nor asthma. She was treated with adrenalin, with prompt recovery. Other cases had been given the same batch of liver extract intramuscularly without untoward results.

INSECT BITES

Two school girls, sisters, were stung by bees. In both cases there was prompt "spasm of the bronchial tree" during which they became intensely cyanosed and went into collapse. One had generalized urticaria and the other did not. Both were treated with adrenalin, with relief.

A man, bitten by a bee, collapsed in the yard before he could reach the house. He had generalized edema with edema of the glottis. This was fifteen or twenty years ago, before the advent of epinephrin. It required several hours for recovery.

A woman standing in the kitchen door was stung by a bee. She collapsed before she could reach the dining room. When reached she was in shock and pulseless. Treatment with adrenalin quickly relieved her. She had a similar experience a second time.

A man was bitten by eighteen or twenty bees, all of the stings being on the right arm. He died after forty-eight hours, following prolonged collapse. At autopsy there was generalized edema in the distribution of the right axillary artery and the right vertebral artery. He developed urticaria soon after he had been stung and this disappeared following epinephrin treatment, but the patient did not recover.

One death was reported from a wasp sting.

One case of shock described as "six plus" was reported from a bed bug bite.

TABLE II

Cases of severe anaphylactic shock or death

Substance Causing Reaction	Mode of Administration or Contact	Shock	Death
	Serums and Antitoxins		
Horse serum	Subcutaneously	3	1
Horse serum	Not known		1
Tetanus antitoxin	Intramuscular	1	
Tetanus antitoxin	Not known	1	
Tetanus antitoxin	Not known		1
Diphtheria antitoxin	Therapeutic	2	
Diphtheria antitoxin	Therapeutic		2
Diphtheria antitoxin	Prophylactic		2
Streptococcus antitoxin	Intravenous	1	
Scarlet fever antitoxin	Not known	1	
Antipneumococcus serum	Not known	1	
	Pollen Extracts		
Ragweed extract	Therapeutic	7	
Ragweed extract	Therapeutic		2
Timothy extract	Therapeutic	2	
Rose pollen extract	Therapeutic	1	
	Extracts for Allergic Testing		
Ragweed	Scratch test	1	
Wood smoke extract	Scratch test	1	
Orris root	Scratch test	1	
Streptococcus vaccine	Intracutaneous	1	
Pure lactalbumin	Intracutaneous	1	
House dust	Intracutaneous	1	
Horse serum (undiluted)	Intracutaneous		1
Annual rare pollen	Intracutaneous	1	
Mule dander	Intracutaneous	1	
Tetanus antitoxin	Intracutaneous	1	

TABLE II (Continued)

Cases of severe anaphylactic shock or death

Substance Causing Reaction	Mode of Administration or Contact	Shock	Death
	Foods by Mouth		
Milk	Ingestion	2	
Eggs	Ingestion	2	
Beer	Ingestion	1	
Wild honey	Ingestion	1	
One cherry	Ingestion	1	
Blackberry pie	Ingestion	1	
Honey	Ingestion	1	
Soy bean	Ingestion	1	
	Drugs		
Quinine	Orally	1	
Aspirin	Orally	3	
Novocain	Intraurethrally		1
Iodized oil	Intraurethrally	1	
Calcium gluconate	Intravenous	1	2
Neoarsphenamin	Intravenous	1	
	Biologicals		
Antuitrin "S"	Subcutaneous	1	
Colon bacillus vaccine	10,000 dose, intravenously	1	
"Brooks hemoprotein"	Subcutaneous	1	
Liver extract	Intramuscular	1	
Pecan extract	Therapeutic	1	
	Insect Bites		
Bee sting	Bite	4	
Bee sting	Bite		2
Wasp sting	Bite		1
Bed bug	Bite	1	
	Transfusion		
Egg in donor's diet	Intravenous	1	
Milk in donor's diet	Intravenous	1	
	Physical Allergy		
Sunlight	Prolonged exposure	1	

TRANSFUSION

The recipient was allergic to egg. The donor ate eggs about two hours before transfusion. After receiving 75 c.c. of blood the recipient experienced severe dyspnoea. He was placed in an oxygen tent and given adrenalin with recovery. Although he had previously had eczema he had never had asthma before. Direct blood matching and matching by groups had shown compatibility prior to the transfusion.

PHYSICAL ALLERGY

A woman extremely sensitive to sunlight was preparing to take a bath. Her telephone which was in an upstairs sun room rang and she proceeded to answer the phone, unclothed. She stood in the direct sunlight talking for some time and then went into collapse.

DISCUSSION

Certain of the cases mentioned are probably not instances of allergic shock. Such are the reaction of anti-pneumococcus serum, which may have been psychic; that to ragweed oil which may have been embolic; that to calcium gluconate which may have been vasomotor; the neoarsphenamin reactions; the reaction to intramuscular liver extract; and the fatal bee sting case which sounds more like a virus or venom death than anaphylactic.

In one or two cases there might be a difference of opinion as to whether we are dealing with severe allergic reaction or true anaphylactic shock.

Such cases are included, however, since they well represent the different types of shock reaction which a physician may at some time encounter following

therapeutic measures. It seems probable that a poll of physicians, sufficiently large to possess statistical value, would show a lower frequency, but the fact that 50 per cent of those interviewed had either seen or had first hand knowledge of severe reactions of this sort, would indicate that they are much more frequent than the literature on the subject would lead us to believe. Although parenteral medication has come into very widespread use and, considering its frequency, is rarely accompanied by untoward results, the risk should be realized and proper precautions should always be employed.

PRECAUTIONS

The precautions which will do much toward preventing untoward reactions are tabulated below as they appeared in the exhibit referred to above.

A B C OF PREVENTION

Allergy Consciousness. Before injecting a foreign substance enquire concerning:

Idiosyncrasy
  Foods, drugs, sera, horses, etc.
Allergic history
  Asthma, hay fever, urticaria, migraine abdominal allergy. (In order of importance)
Family history of outspoken allergy
Previous medications and reactions thereto (especially serums)

Beforehand. Make preliminary diagnostic tests for idiosyncrasy to biologicals:

Skin
  Scratch followed by intracutaneous
Conjunctiva
  Serums and pollens
Mucous membranes
  Drugs, foods, etc.
Subcutaneous
  If in doubt give extremely small dose subcutaneously, and await reaction

Care. Be sure proposed dose is correct
Use an extremity for preliminary injection
Apply tourniquet above injection if allergic reaction ensues
Administer epinephrin in opposite arm

TREATMENT

If shock has occurred. Symptoms:

Severe—within a few minutes
  Collapse
  Death
Moderate—after several minutes
  Sneezing barrages
  Urticaria
  Asthma
  Vomiting
  Diarrhea

First:

Apply tourniquet above site of injection
Inject epinephrin into opposite arm or above tourniquet —repeat if necessary
Provide complete rest
Apply cold to skin if there is urticaria

Later:

When relieved, release tourniquet temporarily
  Reapply on return of symptoms
Keep alternating, release and reapplication until symptoms no longer appear after release

Treatment of obstructive asphyxia. In bronchial asthma and asthmatic bronchitis:

Find and remove offending allergens
Bronchial relaxants
  Epinephrin
  Ephedrin
  Atropin derivatives
Expectorants
Oxygen
Bronchoscopy

In angioneurotic edema of air passages:

Epinephrin
Cold applications
Intubation
Tracheotomy

Diagnosis is important:

"Not all that wheezes in asthma"
Use available aids such as X-ray, bronchoscopy, etc., to be certain that the cause is not
  Foreign body
  Malignancy
  Aneurism
  Infection, etc.

Desensitization. When serum tests are positive, and yet the patient must have serum:

Dilute the serum, serially 10x: 100x: 1000x: 10,000x
Scratch skin with these serial dilutions
Start desensitization with that dilution which just fails to react positively
Give injections hypodermically every half hour
Have epinephrin and tourniquet at hand
Always give desensitizing doses in extremities
Double the strength of dose each time, going up through the several dilutions

If treatment must be given intravenously it is usually safe to start half hourly intravenous injections after one has passed the dose of 2 c.c. hypodermically.

Start the intravenous treatment with one-tenth c.c. or less. It is also well to drop back to a somewhat more dilute extract

Continue doubling the dose until the proper total dose has been administered

The above program holds in most cases

A few who appear to be congenitally hypersensitive to serum, appear not to tolerate even this method of desensitization.

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The Clinical Significance of Indicanuria*

By

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A REVIEW of the literature of indicanuria discloses that much confusion exists. The physiologic chemists do not agree in their conclusions and many clinicians decline to accept indicanuria as a clinical entity. The prevailing opinion among gastroenterologists appears to be that excess of protein in the diet and constipation are the chief etiologic factors. Underhill and Simpson (1) conclude "that phenol and indican excretion bear quite a different relation to one another. That constipation overshadows the effect of diet and causes a large increase in the excretion of both indican and phenol." Meat ingested in large quantities, caused a marked increase in both substances. Morgan (2) noted that indicanuria was greatly increased in typhoid, peritonitis, and cholera. In true autointoxication, indican rarely disappears.

Seyal (3) found no correlation between constipation and indican excretion. Verbrycke (4) considers indolic autointoxication a very real entity, and is independent of constipation. Diet will not alter the condition and acidophilus treatment is useless. Plansker (5) found large indican content in the first and second months of life. Constipation of the patient seems to be the great factor. It is increased in infections and diarrheas. The administration of sugar caused a decrease or disappearance of the indican. Moewes (6) found a large indican content in achylia gastrica patients. Baar (7) recommends high colonic lavage as treatment. Levin (8) excludes meat and eggs, and feeds a diet consisting of cereals, vegetables, fruit and milk. Because of lack of space, I omit many references.

My object in this paper is to present my own clinical experience. In the year 1917, I determined that each patient's urine should be examined for indican regardless of the nature of the illness.† The urine voided during the night from bedtime to breakfast was selected. Obermayer's test was employed, designating one, two, three and four plus reactions. The number of patients examined since that time is 18,006. For the purpose of this study only those cases showing a "four plus" reaction were utilized inasmuch as it is exceedingly rare to find a specimen of urine that does not show "one plus," and I wish to present only the strongly positive reactions. 15% (2700) of the total disclosed a 4 + indican reaction. Intensive study of this list of cases revealed that patients suffering from practically every disease were included in the 4 + reactions. However, it gradually became evident that certain diseases predominated, *e.g. achylia gastrica, duodenal ulcer*, and *"toxic" headache.*

The *achylia gastrica* cases numbered 530. All of these patients were subjected to fractional stomach content analyses. Of this number 98% revealed indican 4 +. Dietetic treatment and exhibition of full doses (4 c.c.) dilute HCl. corrected digestive symptoms and greatly improved the patients' general nutrition but had no effect in diminishing the indican content of the urine.

The *"toxic" headache* cases numbered 696. Headaches due to nasal sinus conditions, eye disorders, syphilis, arterio-sclerosis, allergy, hypertension, etc., were excluded from this list. 85% revealed the presence of 4 + indican. But 10% of the patients in this class were affected with constipation. The headaches were periodical in character usually accompanied by nausea, often vomiting, bad taste, and general depression. Vertigo and mental sluggishness were frequent complaints—in brief, the symptoms usually ascribed to "intestinal toxemia" or "biliousness." The dietary habits and food discriminations of the patients were studied and finally the following *empiric diet-list* was evolved.

*From the Soper-Mills Clinic.
†This work has been carried out under the supervision of my chief technician, Miss Cornelia Taylor, to whom I am greatly indebted for her faithful and conscientious assistance.
Submitted May 27, 1935.

DIET LIST‡

Breakfast:
Fruit, raw and cooked
Cereals with cream and sugar
Coffee

Lunch:
Choice of all fruits, raw and cooked
All vegetables, raw and cooked
All kinds of breads with butter
Salads—French dressing
Cheese and crackers
Desserts—fruit and fruit ices

Dinner:
Roast, broiled and stewed beef, lamb and fowl
Baked or broiled fish
Potatoes or rice
Choice of green vegetables. Salads
Choice of bread, rolls, muffins and butter
Desserts—fruit and fruit ices

Special caution:
Use sugar sparingly
Use salt in moderation
Eat an excess of fruit and vegetables

It will be observed that eggs and rich desserts particularly egg and milk combinations are excluded from the dietary. This regimen is extremely useful and in many cases brilliant results were secured, however, diminution of the quantity of indican in the urine was a rare occurrence. Many of these patients are benefited by periodic (every two weeks) dose of one to two grains of calomel at bedtime followed in the morning by magnesium sulphate solution. A family history of periodic headaches was secured in the vast majority of these patients. Regulation of colon function and general hygienic supervision such as control of habits, exercise, rest, etc., are valuable adjuncts in the therapy of indicanuria or intestinal toxemia.

The cases of *Duodenal Ulcer* numbered 1320. 60% of these patients had 4 + indican reactions. Dietetic treatment, of course, was exactly the opposite to that advised in the toxic headache patients, the diet consisting largely of milk and egg combinations. The indican was also persistently present despite treatment. Many patients, observed after complete healing of the ulcer, milk and eggs being excluded from the dietary, continued to show a 4 + indicanuria.

As to constipation being a factor, I have records of six cases of megacolon with fecal retention of a week or more, which disclosed but faint traces of indican in the urine. Irregularity of dejections and complaint of gas pressure were the usual features. A majority of these patients employed enemas and cathartics in an effort to secure relief from the subjective symptoms.

Five cases of colectomy for ulcerative colitis and general polyposis were studied. Prior to the operation a 4 + indican was present in the urine of all of these patients. Some months or years later when good restoration of health had occurred, urinalysis failed to disclose a trace of the former large indican content.

Forty-two individuals in good health with no complaint of digestive disorders, headaches or vertigo, were found after a health audit to show 4 + indican reaction in the urine.

TREATMENT

I have employed all the methods suggested by various clinicians and experimentalists, including Bulgarian culture milk, acidophilus milk, Soricin, various intestinal antiseptics, exclusion of meat from the diet, only to abandon them as useless as far as diminution in the indican content of the urine is concerned. These methods also failed to give the patient symptomatic relief. The diet-list given above with periodic doses of calomel and magnesium sulphate has been useful in relieving symptoms. Some patients show a decrease in the indican content after a long course of mineral oil retention enemas. Cases of ulcerative colitis at times reveal a diminution of the indican after prolonged internal use of large doses of bismuth subgallate.

‡The list is of course subject to modification in conformity with requirements of the individual patient.

COMMENT

It is obvious that achlorhydria might inaugurate defective chemical digestive processes that would eventually result in the production of large amounts of indican. The starch granule is not broken up, as noted in the poor chymification of the Ewald-Boas testmeal. The connective tissue from a meat meal may be largely recovered from the feces. Furthermore, more intensive study of the achylia gastrica list of patients disclosed that few of them suffer from the symptoms usually present in the "toxic" headache class.

The large percentage of 4 + indican patients in the duodenal ulcer list presents a problem more difficult to explain. The digestive process is good in duodenal ulcer, and no such defect exists as in achylia gastrica. We must consider that the remaining 40% of the duodenal ulcer patients do not present excess of indican in the urine.

Perhaps the class of patients who remain symptomless regardless of indicanuria are endowed with more stable nervous systems, and develop immunity or resistance against the toxic elements. The larger less-favored class which is susceptible to the toxin, suffer from the toxic headache syndrome and are predisposed to the development of duodenal ulcer.

CONCLUSIONS

1. The term "indican dyscrasia" is employed inasmuch as the evidence indicates an inherited tendency, and its persistence in the individual confirms the view that it is a constitutional disorder.

2. A trace or 1 + indican reaction is rarely absent in any specimen of urine. Therefore, this study includes only the strong 4 + reaction which is termed "indicanuria."

3. Indicanuria may be found in practically all diseases, but is present in a large percentage of patients affected with duodenal ulcer, achylia gastrica, and "toxic" headache.

4. Indicanuria (and such symptoms as may be attributed to it) is amenable to general dietetic and hygienic treatment, but the reaction in the urine remains 4 + regardless of improvement in the patient's condition.

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SECTION V—*Therapeutics*

The Pathology and the Treatment of Intestinal Amebiasis*

By

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IT is a curious fact that a disease which affects from 5% to 10% of the general population should be largely unknown to or ignored by a great proportion of the medical public. Yet this was the case with amebiasis up to the time of the Chicago outbreak. In part this was due to the widespread belief that the disease was restricted to the tropics and the subtropics. In part it resulted from the erroneous conception, created by common nomenclature, that dysentery constitutes one of the outstanding clinical features of the infection. And in part it was the result of the difficulty if not the impossibility of establishing the diagnosis experienced by the untrained observer.

Outside of the southern states it is doubtful if more than a small proportion of practising physicians are aware of the extremely varied clinical pictures which amebiasis may induce. Even when the infection is recognized there is too often a tendency to minimize its importance if acute symptoms are lacking. It is unnecessary to emphasize to anyone familiar with the disease the fallacies of this view. Infestation is invariably associated with tissue damage. Serious complications may arise without antecedent dysentery or even diarrhea. There is a real danger to immediate contacts especially if the infected person be a housewife concerned with the preparation of food for her family (1).

Discussions of treatment, however, frequently are pessimistic concerning eradication of the infection although it is recognized that acute symptoms often may be controlled with relative ease. There is frequent mention of recurrences and so called resistant cases. It is probable that these difficulties may be explained in one of several ways. The results of therapy in endemic areas are necessarily unsatisfactory unless reinfection can be prevented. Knowledge of the detained pathology is too infrequently the basis of the therapeutic plan. Choice of the available amebicidal drugs is not based upon their differing pharmacologic actions.

The not uncommon asymptomatic cyst-passer has created the impression that the *endamoeba histolytica* may exist in the human intestinal tract as a harmless commensal living in symbiosis with the host. Careful pathologic studies, however, have demonstrated the fallacy of this concept. This ameba is invariably a true parasite. Its presence is always associated with actual tissue damage, at the least, localized destruction of the superficial epithelium (2). In the milder cases this may not be evident without the aid of the microscope. In the advanced cases there is extensive and deep ulceration with widespread destruction of the mucosa. Clinically these two extremes represent the symptomless carrier and the serious case of acute amebic dysentery. Between these two pathologic extremes lie the varying degrees of tissue destruction and invasion which are attended by the atypical clinical phenomena which constitute the composite picture of intestinal amebiasis.

The infection is transmitted by the ingestion of the encysted forms in food or drink. These pass through the stomach and upper small intestine to the terminal ileum or colon where excystation occurs and a single four nucleate ameba is released. Subsequent development produces an eight nucleate organism which then divides by fission into eight motile trophozoites each possessing a single nucleus. These motile forms, or trophozoites, then attack the mucous membrane of the intestine, in part by a cytolytic substance which they secrete, and in part by mechanical penetration of their pseudopodia (3). This combined action enables them to destroy the superficial epithelium and to enter the deeper tissues producing the ulceration which constitutes the essential pathology of amebiasis. The lesions are restricted to the colon except in rare instances when the ileo-cecal valve and adjacent ileum may be involved associated with extensive invasion of the cecum. They may occur throughout the colon or be limited to certain areas. The commonest sites in the order of frequency are the cecum, ascending colon, rectum, sigmoid and appendix. When the ulceration is localized, the cecum and ascending colon are much more frequently affected than the rectum or sigmoid (4).

The initial lesion consists of superficial destruction of the mucosa without appreciable invasion of the deeper tissues. This is believed to be due largely to the action of a cytolytic substance secreted by the amebae. At first the amebae lie only on the surface and in the lumens of the glands. The immediately adjacent epithelial cells degenerate, become necrotic, and disappear leaving a denuded stroma. The gland crypts are stripped of their epithelium and in many instances packed with masses of trophozoites. This is accompanied by localized hyperemia but without other

*Presented at the Postgraduate Course in Gastro-intestinal Diseases, Duke University Hospital, Durham, North Carolina, Nov. 1, 1935. Submitted May 2, 1936.

evidence of inflammation. Lesions of this type are almost certainly continually occurring in every carrier of the parasite but rapidly healing if the individual's resistance is effective.

As multiplication of the amebae and progressive epithelial destruction occur, there is invasion of the interglandular tissue and of the submucosa where they are to be found lying singly or in groups. The immediately adjacent tissue is cytolysed and amorphous. There is complete absence of polymorphonuclear infiltration and of signs of suppurative inflammation. Not infrequently lymphatic channels and small veins may be observed containing amebae within their lumens. With penetration into the submucosa, peripheral invasion of normal tissues occurs, progressively increasing the area of necrosis. Thrombosis and destruction of blood vessels impair the nutrition of intact overlying mucous membrane contributing to subsequent ulcer formation. Although the muscular coats of the intestinal wall offer a barrier to the deeper invasion of the amebae, this resistance is relative only. Extension into the muscularis occurs with degeneration and lysis of the muscle fibers, and with the amebae lying singly or in nests throughout the affected zone. Lacking effective resistance on the part of the host, or adequate treatment, the invasion may continue deeper ultimately to reach the peritoneum and to lead to perforation.

The peripheral extension of the infection in the submucosa leads to the formation of a minute abscess cavity roofed by anatomically if not physiologically intact mucous membrane. Rupture of the abscess into the lumen of the intestine then produces the characteristic "flask shaped" ulcer of amebiasis. When these ulcers are numerous and in close apposition, the peripheral invasion of the amebae beneath the mucosa tends to make them confluent and to form the larger open ulcers so commonly encountered in this disease. Microscopic sections taken through such an area present a somewhat different appearance because of the inevitable secondary bacterial infection. Immediately adjacent to the ulcerated area the submucosa is thickened by edema, engorgement of capillaries, lymphocytic infiltration, and proliferation of connective tissue cells. The signs of tissue necrosis become more prominent as the area of ulceration is approached. The nuclei, swollen and pyknotic at the periphery, more centrally have disappeared, and the normal structure of the tissue is destroyed. In the zone of necrosis the amebae are seen scattered or in groups, often lying within veins or capillaries. In areas where bacterial invasion has occurred there are masses of polymorphonuclear leucocytes. The actual walls of such an ulcer are formed by the necrotic or degenerating remnants of the mucosa and submucosa or deeper structures if these have been involved.

Although the essential lesion produced by *endamoeba histolytica* is lysis without suppuration, secondary bacterial infection invariably occurs and may greatly alter the primary pathologic picture. Thus when there has been extensive loss of the mucous membrane there may be many areas where suppurative inflammation with dense collections of leucocytes and even discrete pyogenic abscesses predominate.

Healing of these ulcers occurs from the periphery and, in the case of the smaller ones, is complete and without scar formation. The stimulus to connective tissue proliferation however, results in extensive and often deforming scars at the sites of the larger ulcers.

The gross pathology of the colon varies greatly. All stages from the earliest and most superficial erosion of the mucosa to deep, even perforating, ulcers may occur together. The carrier even in the absence of dysentery or diarrhea may present not only the superficial lesions but deep ulcers as well. The clinical picture which accompanies this infection is not the expression of a particular stage in the pathology. It is the result of the extent of the lesions in the colon together with the effects of secondary bacterial invasion.

In the early preulcerative stage the mucosa presents minute hyperemic and hemorrhagic areas where superficial cytolysis has occurred. The early stages of invasion and lysis of the mucosa and submucosa give rise to minute congested nodular areas projecting from the tops of folds of the mucous membrane. Some of these may show small openings through which a gelatinous fluid may be expressed which contains numbers of the motile forms of trophozoites of endameba histolytica. With deeper and peripheral extension of the necrosis both the opening and the cavity are enlarged to form the typical "flask" ulcer. The surrounding mucosa is congested and hemorrhagic. The edges are ragged usually and the base composed of sloughing necrotic tissue. Certain of the smallest ulcers, however, which are confined to the mucosa may have a punched-out appearance with sharp edges and comparatively smooth and clean bases. These small ulcers are usually round or oval in shape.

The larger ulcers are usually irregular in outline and extend into the muscularis or even deeper. They result from the peripheral extension of the amebae through the submucosa and the coalescing of smaller ulcers to form one large confluent process. These are characteristic in appearance with irregular, raised, shaggy, and undermined edges. In a recent process the floor is composed of necrotic material, pus and blood; in the older ones the floor is relatively clean. The burrowing of the amebae frequently leads to sinus formation beneath the mucosa.

In advanced and serious infections this same characteristic may cause extensive sloughing of the mucosa and serious hemorrhage. It is obvious in such a case that healing must be accompanied by extensive scar tissue formation and permanent deformity of the colon.

The frequent invasion of radicles of the portal system in the intestinal wall indicates one of the routes by which the amebae may reach the liver. With infection of this organ the adjacent hepatic cells undergo cytolysis. Peripheral extension occurs, with surrounding hyperemia, lymphocytic infiltration, hemorrhage, and connective tissue proliferation. At this stage the gross specimen presents small grayish brown moth-eaten areas in which the normal structure has disappeared. The development of true abscess of the liver results from coalescing and extension of many of these small zones of necrosis. Unless bacterial infection has occurred the contents of the cavity are characteristic—a thick grumous material having much the appearance and consistency of anchovy sauce. The connective tissue of the liver is resistant to lysis by the amebae. Condensation of the supporting structure of the organ and new formed connective tissue tend gradually to limit the extension of the necrotic process and to form the dense fibrous wall which is found in the old amebic

liver abscess. Section through such an abscess wall shows an inner zone of more or less cytolysed necrotic material containing amebae, mononuclear cells, fibrin and erythrocytes. Immediately adjoining this is a zone of active connective tissue proliferation infiltrated with lymphocytes, and surrounded by a dense layer of fibrous tissue. The adjacent liver parenchyma is hyperemic and may show capillary hemorrhages.

Study of the pathology of the disease thus demonstrates that the amebae are to be found simultaneously in three different situations. They are present in the colonic contents which they may leave to attack the mucosa. They are present on the surface of the mucous membrane and in the lumens of the glands in the earliest lesions where they destroy the superficial epithelium. In the older lesions they are deeply placed in the tissues of the intestinal wall and not in contact with the intestinal contents. Since this condition presumably exists in the majority of individuals infected by endamoeba histolytica, it is possible to formulate an axiom of therapy. In order to achieve complete eradication of the infection, it is imperative simultaneously to expose the amebae in the intestinal contents, on the surface of the mucosa, and deep within the tissues to lethal concentrations of an actively amebicidal drug.

THERAPY

Some of the numerous therapeutic preparations available are effective in sterilizing the intestinal contents. Others are effective against the amebae in the tissues. However there is no single one which completely fulfills the three fundamental therapeutic indications. This can be accomplished only by combined therapy.

The drugs generally in use for the treatment of amebiasis fall into four groups: the alkaloid of ipecac, emetine and its compounds; organic arsenicals; oxyquinoline derivatives; and compounds of bismuth. Since these vary not only in their pharmacologic actions, but in their usefullness and their dangers, it is desirable to discuss them briefly.

Emetine probably is the most widely known of these drugs. It is used hypodermically as the hydrochloride, and by mouth as the bismuth iodide or the periodide. The latter have no advantages over the hydrochloride. Their use involves the same dangers and in addition they are prone to cause severe nausea and vomiting. Whether given parenterally or by mouth the drug is absorbed and is lethal for the amebae in the tissues. It is excreted slowly by the intestine and the kidney and in consequence too long-continued dosage carries the hazard of cumulative toxic effects. Emetine is a protoplasmic poison which in overdosage acts primarily upon cardiac muscle to produce myocardial degeneration, necrosis and scarring.

Because of its prompt effect in controlling the acute symptoms of amebic dysentery it has enjoyed an undeserved repute in the treatment of intestinal amebiasis. Craig (5) has reported that eighty-five per cent of his cases treated by emetine alone showed continued infection. Yet its direct and efficient action upon the amebae within the tissues makes it one of the most important of all the amebicidal drugs. Because of the dangers of cardiac damage, individual doses of the hydrochloride should not exceed a millogram per kilo of body weight per day, and the total dosage should not be in excess of ten milligrams per kilo. This drug should be used with great caution if at all in the presence of organic heart disease.

Various compounds of arsenic have been widely used. Like emetine they are not completely efficient amebicides. Acute or chronic arsenic poisoning are not rare sequelae. Particularly is this true of stovarsol and treparsol. Recently a less toxic arsenical, carbarsone, has been developed which is more actively amebicidal (6, 7). It is absorbed from the gastrointestinal tract and excreted in the urine. It is administered orally in dosage of 0.25 gm. twice daily for ten days and may be used in 2 per cent solution for retention enemata. This drug is contraindicated in the presence of hepatic and renal disease.

The oxyquinoline derivatives contain approximately 28 per cent of iodine which is excreted in the urine. They are available under a number of trade names, yatren, quinoxyl, anayodin and chinofon (N.N.R.). These preparations have little if any toxicity although they appear to be somewhat irritating to the intestinal tract, in certain individuals increasing or producing diarrhea. This side effect can usually be controlled by rest or by small doses of opium without the necessity for reduction of dosage. They are actively amebicidal (8). However their action seems to be restricted largely to the amebae in the intestinal contents and on the surface of the mucosa since none of them are effective in the case of amebic abscess of the liver. These preparations are supplied as enteric coated pills each of .25 gm. From two to four pills are administered orally three times daily before meals for eight to ten days. They may also be used in 1 per cent of 2.5 per cent solution for retention enemata. The solution should be freshly prepared and not heated since this leads to decomposition of the drug.

A somewhat similar compound, iodochloroxyquinoline, vioform (N.N.R.) contains about 40 per cent of iodine and about 12 per cent of chlorine. It is said to be a more effective amebicide than the other oxyquinoline derivatives (9). Animals killed by a large single dose, however, show some degree of liver necrosis. Consequently this drug should be used with caution when there is evidence of hepatic damage. It is supplied in capsules containing 0.25 gm. each and should be given in two courses of 0.75 gm. daily for ten days with a week's rest between. This compound is irritating to the rectal mucosa and cannot be used for retention enemata.

Various preparations of bismuth have been used in the treatment of amebiasis with the dual objective of eliminating the amebae and of controlling severe diarrhea and dysentery. Their amebicidal activity is low and there is little reason now for their inclusion in the group of specific drugs.

In considering the problem presented by the individual who is infected by *endamoeba histolytica* it has been customary to make an arbitrary distinction between acute dysentery and diarrhea on the one hand and the relatively asymptomatic cyst passer on the other. Different therapeutic measures are discussed for each group as though the principles involved differed fundamentally. Therapeutic failures are too often the result of rule of thumb methods. The known pathology of the disease is ignored. The necessity for simultaneous and effective attack upon the amebae in the intestinal contents, on the surface of the mucous membrane, and in the tissues of the intestinal wall is forgotten. To be efficient, treatment must accomplish

two ends. It must relieve the patient of his immediate symptoms, and even more important it must completely eliminate the infection. If it is recalled that the symptomless cyst passer may have actual ulceration and invasion of the wall of the colon it must be apparent that the carrier and the case of acute dysentery present fundamentally similar problems.

Since no single drug is completely efficient, protozoologic, in contradistinction to clinical, cure necessitates the use of combined treatment. Emetine, which acts primarily upon the amebae in the tissues and little if at all upon those in the intestinal contents, is indispensible, especially during the periods of diarrhea or loose stools. One of the preparations which is little absorbed must be used simultaneously to eliminate the amebae in the contents of the colon and on the surface of the mucous membrane. One of the oxyquinolin derivatives will accomplish this end.

The patient with acute dysentery must be kept strictly in bed. The fluid intake should be large. The diet should be soft or fluid and relatively high in protein and low in carbohydrate. Severe pain, cramps, tenesmus and diarrhea can be controlled by repeated small doses of opium as the camphorated tincture. One milligram per kilo of body weight of emetine hydrochloride is given subcutaneously or intramuscularly each day for eight days. The intravenous route should not be used. During this same period, anayodin or one of the other oxyquinoline derivatives is given in full dosage by mouth. Each morning following a cleansing saline enema eight to ten ounces of a 2 per cent solution is given by rectum and retained as long as the patient is able.* During its administration the foot of the bed should be elevated and the patient should be turned progressively from the back, to the left side, to the back and to the right side to aid distribution of the solution through the colon. Following this period of active treatment proctoscopic examination as well as change in the symptom picture usually indicates healing of the lesions. There is no specific means of treating the secondary bacterial infection. This phase of the problem can only be approached by improving the general nutrition of the patient, correcting anemia by massive dosage of iron or by transfusion if necessary, and by recourse to such other supportive measures as are indicated. Convalesence should be prolonged until both proctoscopic examination and barium enema indicate that healing is complete. (Barium enemata should be employed most cautiously during the "active stage" of the ailment).

The cyst passer whose symptoms are less urgent may be allowed more latitude. (However, it should be remembered that such patient is the one who spreads the disease; prophylosis towards his contacts is here of the greatest significance). A large percentage of these individuals undoubtedly has only superficial lesions in the mucosa without deep invasion by the amebae. The enlarged forms of themselves are capable of causing little or any organic damage. Many of these patients respond to one or more courses of carbarsone or of any of the oxyquinoline preparations. In others, however, subsequent stool examinations indicate continued infection. This must be accepted as presumptive evidence of more extensive lesions and of deeper invasion of the wall of the colon. And it constitutes an indication for recourse to the intensive method of combined treatment.

It is the writer's practice when dealing with the problem of the cyst passer to explain in detail the hazards of the infection and the limitations of ambulatory treatment. If the patient so elects ambulatory treatment is tried, using carbarsone or one of the oxyquinoline drugs by mouth. No limitations of activity are required although the patient is warned against the use of alcohol and cautioned to avoid roughage in the diet. If, however, this approach proves ineffective, the patient is hospitalized for ten days and subjected to combined treatment. This method of dealing with the problem of intestinal amebiasis has given excellent results.

Although amebic abscess of the liver constitutes a large subject by itself, it may not be amiss briefly to refer to certain aspects of treatment. If the pathology is not complicated by bacterial infection, emetine in adequate dosage will sterilize the abscess cavity, prevent its further extension, and destroy viable trophozoides which may be present in other areas of the liver. The problem then resolves itself into the question as to whether or not the patient is able to absorb the necrotic contents of the cavity without further assistance. Falling temperature, diminishing leucocytosis; and progressive diminution in the size of the liver are favorable indications. When the mass of necrotic and cytolysed tissue is too great, removal of the contents by surgical methods is necessary. In the case of a large right lobe abscess simple aspiration of the contents frequently suffices. Needling of the left lobe however is hazardous because of the proximity of the pericardium. When an abscess has become infected by bacteria open operation and drainage are essential.

Whatever the obvious site of infection it cannot be emphasized too strongly that two fundamental objectives must be reached: clinical cure—the patient must be relieved of his symptoms; protozologic cure—the patient must be freed of his amebae. To accomplish these ends the pathologic anatomy must be visualized and the actions of the various available drugs must be understood. To insure effective treatment every patient should be kept under observation for one to two years. During this period careful stool examination must be made on three or four consecutive days every two or three months. The patient may be assured of complete cure only at the end of such a follow-up period during which there has been no indication of persistent infection.

*Many protozoölogists decry the employment of enemata of any nature. Certainly, if an enema be given, one should employ a solution at a temperature of 105°-110° F. after the suggestion of DeRivas, (Univ. of Pennsylvania), whose experiments demonstrated that such temperature is the thermal death point of the protozoa.—Editor.

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Pectin as a Detoxication Mechanism**

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PRIOR to 1929, very few attempts had been made to distinguish between *available* carbohydrate which can be utilized and metabolized, and *unavailable* carbohydrate. The former consists of starch and soluble sugars sucrose, glucose and fructose. The latter is composed chiefly of hemicelluloses and fiber or cellulose. While the chief value of the available carbohydrate resides in its coloric equivalent, very little, if any, value, aside from its ability to form bulk, is attributed to the unavailable carbohydrate.

In 1929, the British Medical Research Council made available, through the work of R. A. McCance and R. D. Lawrence, tables giving the available carbohydrate values of many fruits, nuts and vegetables (1). These tables have been further supplemented by Widdowson and McCance (2) and by Bell, Long and Hill (3). While the chief value derived from the efforts of these workers lies in focusing the attention of nutritional workers on direct methods for determining the physiologically available carbohydrate of common edibles, sight should not be lost of possible values other than caloric that may be attributed to other factors resident in the foods eaten. In this connection, it is not the purpose of this report to direct attention to the well-established values of the various vitamins and minerals, but rather, to focus interest upon those carbohydrates, the hemicelluloses and cellulose, which have all too bruskly been put aside as of no value at all except for the possible advantage of bulk.

The medical world is persistently, although somewhat belatedly, attempting to check an all too common overindulgence in such foods as spinach and bran. Attention is being called to the spastic or irritable colon as one of the effects of too much roughage.

Cellulose and cell membranes are popularly supposed to add bulk to the feces by virtue of their indigestibility and thus to counteract constipation by stimulating the wall of the gut to contract. With very high and experimental cellulose diets the bulk of the residue is an important stimulating factor, but with average amounts quantitative considerations show that it can be only of minor importance. The average amount of cellulose, insoluble pentosans and cell membrane eaten daily is about 12 grams (Rubner). Fully half of this material is digested and never reaches the feces. The remainder is insoluble in water and incapable, therefore, of binding water so that this material can only increase the feces by about two per cent, not nearly enough to effect the bulk. Rubner found that a man eating 519 grams of the finest wheat bread excreted feces daily weighing about 120 grams (wet weight). The addition of 50 grams of cell membranes in the form of powdered straw led to an excretion of feces weighing nearly 300 grams, but only 37 grams of these were cell membrane. The rest was made up of cell detritus and products of glandular activity, including water. It is this mixture of substances that caused the increased bulk of the feces. Possible unabsorbed products of fermentative digestion of these cell membranes play a part in the increase.

This stimulation of the intestinal glands is not merely a function of the irritation caused by the insoluble material of the cell membranes. Fruits and vegetables, for example, cause a very large increase of detritus, etc., in feces and yet the cell membranes are relatively well digested and contribute little bulk to the feces. It would seem as though some chemical extract or product of decomposition were the chief stimulant. Very little is known of this subject and it appears to be one on which research might be well repaid. McCance and Lawrence conclude the above discussion by saying, "It is therefore chiefly by virtue of the gland stimulation that cell membranes exert a laxative action. Clinical observation could never have brought out this point, for it could never have differentiated between mere mechanical stimulation leading to increased transit and loose motions of large bulk, and stimulation of the mucus and other glands leading to increased bulk, and this, in turn, to increased transit."

The purpose of this report is to describe experiments which are believed to add more light to the action in the body of certain derivitives of the so-called *unavailable* carbohydrate, namely the hemicelluloses and pectins. In recent years, O'Dwyer (4) and Norris and Schryver (5) have shown that from plant material at least two hemicelluloses can be extracted which, upon hydrolysis, yield glucuronic and galacturonic acid. These two sugar acids exist in combination with the two pentoses, xylose and arabinose. In fact, the latter pentose, arabinose, together with galacturonic acid form the basic part of the pectin molecule. The pectin molecule is now believed to give rise to 8 galacturonic acid molecules. It has been well known for the last fifty years that glycuronic acid plays a very prominent role in the detoxication mechanisms of the body. In the body, it is said never to exist in the free state but in combination in such materials as mucin, chondroitin, heparin (6), etc. It is constantly excreted in normal urine in small amounts conjugated with aromatic alcohols, phenols, ketones, acids, etc.,

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which are either products of metabolic activity, bacterial activity in the body or the presence of various toxic materials in the ingesta. For the last three years in this country and for some ten years prior to this in Germany, raw apple pulp has been used with great success in the treatment of infantile diarrheas and dysenteries. Of the various constitutents of the apple, pectin seemed to be the most logical component to which the greatest part of the therapeutic value could be ascribed. It possesses the properties of a hydrophilic colloid with great adsorptive qualities. Furthermore, it is capable of giving rise to galacturonic acid upon being broken down. The question naturally arose as to whether or not this uronic acid acted similarly to glucuronic acid as a detoxicating mechanism. Malyoth (7) was of the opinion that it would. This report provides evidence that such indeed is the case.

For the purposes of this experiment six rabbits were used. They were so selected that their weights were as nearly identical as possible. They were separated into three groups of two each. Each rabbit was placed in a separate metabolism cage in order that the total urine output could be obtained. For three days the rabbits were fed oatmeal ad libitum. It was hoped by this means to replace foods of variable and uncertain constitution by a food of uniform and known composition. The reason for this was based on preliminary experiments in which it was found impossible or very difficult to deplete rabbits of their glycuronic acid reserves when green foods were ingested. Miller and Conner (8) and Biberfeld (9) also observed that rabbits could tolerate larger doses of menthol if fed greens. The fluid intake was limited to 100 c.c. of Ringer's solution given three times daily by stomach tube. One group of two rabbits received in Ringer's solution one gram of pectin. Beginning with the fourth day, these two rabbits together with two others, were each given one gram of menthol. On the fifth day, the menthol was increased to 1.33 grams, on the sixth day to 1.66 grams and on the seventh day to 2 grams. This provided for a total daily consumption of 3, 4, 5 and 6 grams of menthol.

Each morning the twenty-four hour collection of urine was measured and recorded. Urea and uronic acid determinations were made on aliquot portions. The uronic acid was determined by two methods. One was that described by Bang (10) modified to use the Shaffer-Somogyi copper reagent. The second method was that described by Link (11). Urea was determined colorimetrically by the use of Nessler's reagent. The results of these determinations were recorded as milligrams per rabbit per day. (Table I).

The evidence upon which is based the contention that galacturonic acid (pectin) can be utilized by the organism in detoxicating menthol, is found in the urea and uronic acid excretion. The first day of menthol administration followed a period of three days in which two of the rabbits receiving menthol had been getting also three grams of pectin daily. This provided an opportunity for creating reserves. The results for the first day show that the rabbits receiving pectin in addition to the menthol excreted nearly three times as much uronic acid as the rabbits getting menthol only. The total average excretion of uronic acid by the pectin-fed rabbits was 25 per cent greater than that of the rabbits fed menthol only.

Furthermore the protein breaktown in the pectin-fed rabbits was less, indicating a protein-sparing action on the part of pectin. On the second, third and fourth days, the rabbits receiving menthol only exhibited an increasing protein catabolism while the animals getting the pectin in addition to the menthol showed very little if any variation in the protein breakdown. The rapidly increasing metabolism of endogenous protein in the group receiving menthol only permitted a great increase in uronic acid production, great enough, in fact, to exceed, on the last day only, the uronic acid production of the group getting pectin. In view of these results, the sole source of uronic acid cannot be entirely from the glucogenic amino acids liberated by endogenous protein catabolism. The administration of preformed uronic acid

TABLE I

Date	Feeding	No. of Rabbits	Vol. of Urine in c.c.	Nitrogen	N cal. as urea	Uronic acid by CO_2	Uronic acid by Reduction	Amounts Given
5/ 7/35	Oatmeal	6	780	2.128	592.0	645	86.0	
5/ 8/35	Ringer's	2	290	2.439	757.2	——	——	
	Menthol + Ringer's	2	250	1.342	359.0	505	97.5	3 gms. menthol
	Menthol + Ringer's + Pectin	2	260	1.170	325.5	1596	266.5	3 gms. menthol + 3 gms. pectin
5/ 9/35	Ringer's	2	295	1.476	217.7	——	——	
	Menthol + Ringer's	2	240	3.331	856.2	1843	673.9	4 gms. menthol
	Menthol + Ringer's + Pectin	2	320	2.596	888.8	2158	798.4	4 gms. menthol + 3 gms. pectin
5/10/35	Ringer's	2	200	2.716	581.2	——	——	
	Menthol + Ringer's	1	125	3.922	1040.1	715	410.0	4.66 gms. menthol
	Menthol + Ringer's + Pectin	2	230	3.704	911.6	1858.4	686.6	1.66 gms. menthol + 3.45 gms. pectin
5/11/35	Ringer's	2	420	2.716	577.6	——	——	
	Menthol + Ringer's	1	250	2.758	1473.4	3130 0	1002.5	3.33 gms. menthol
	Menthol + Ringer's + Pectin	2	380	2.094	851.4	2622.0	978.6	3.33 gms. menthol + 3.75 gms. pectin

TABLE II

Day	No. of Rabbits	Vol. of Urine	N as urea mgs.	Uronic Acid by CO_2	Uronic Acid by Reduction	Amounts Fed	Cause of Death
I	6	1410	260	2086	543	2 gms. menthol	
II	6	1340	270	1894	226	2 gms. menthol	
III	5	920	280	1140	156	2 gms. menthol	Edema of Glottis
IV	5	750	80	1734	549	2 gms. menthol + 4 gms. chondroitin	
V	2	350	180	3066	766	2 gms. menthol + 4 gms. chondroitin	Diarrhea

provides a better source of detoxicating material since it conserves body protein.

A comparison of the average urea excreted by the three groups during the experimental period shows that the groups receiving Ringer's solution only excreted the least. These animals were on a purely starvation basis. The rabbits getting menthol only excreted 75 per cent more urea while those receiving both menthol and pectin were intermediate, excreting only 40 per cent more. A comparison of body weight losses shows the same relationships. Thus both groups getting menthol catabolized more body protein than the group on the starvation basis. Menthol therefore stimulates the breakdown of body protein. This may be taken as an illustration of what is meant by the toxic breakdown of this material. Pectin is able to reduce this effect.

This experiment, which is typical of many, demonstrates the fact that galacturonic acid is capable of forming conjugation products with toxic materials in the same manner as glucuronic acid. In addition, it shows that pectin in as small daily doses as three grams exerts a definite protein-sparing action. This work definitely establishes for the first time the nutritive value of pectin and places additional importance upon those foods which are good sources of this material.

In view of the importance of these findings, it was deemed advisable to determine the reliability of the method used by testing the detoxicating value of chondroitin, a substance containing glucuronic acid as the prosthetic portion of the molecule.

For three days, six rabbits were given two grams of menthol. They were allowed no food. Table II shows that during this period there was a marked decrease in uronic acid output. There was also a gradual increase in protein catabolism. Beginning with the fourth day, four grams of chondroitin was administered along with the menthol. Immediately there resulted a marked increase in uronic acid output and a diminution in protein breakdown. By the second day of chondroitin feeding, diarrhea had become so severe that three of the rabbits died. The experiment was therefore discontinued. There can be no doubt, however, that chondroitin is effective in combating menthol intoxication and that the method employed is capable of conclusively demonstrating this.

As noted above, chondroitin is capable of causing a marked increase in intestinal activity. This was noted by Crandall (12) also. Work in this laboratory with pectin showed that it, too, has marked stimulative properties. In fact, one rabbit died from intestinal gangrene developing as a result of an intussusception involving 10 centimeters of gut. Ivy (13) has noted the laxative influence of mucin. These three materials resemble each other chiefly in their uronic acid components. It does not seem reasonable that the laxative effect is due to the protein fraction. Perhaps the laxative effect of the hemicelluloses and pectins noted previously is due to their uronic acid content.

The rabbits dying from menthol intoxication exhibited gross lesions exclusively limited to the mucosa of the gastro-intestinal tract. Ulcerative and hemorrhagic defects were commonly found in the stomach, duodenum, gall bladder, small and large intestine. The uniform nature and distribution of these lesions is suggestive either of a disturbance of mucin synthesis or an excessive breakdown once it is formed. In either event it appears that the demand for glucuronic acid is so great that the body cannot supply an amount adequate for detoxication purposes and, at the same time maintain a normal gastro-intestinal mucosa.

In this connection, it seems pertinent to add that any defect in the ability of the body to conjugate uronates as, for example, liver injury; any reduction in the intake of preformed uronic acid or an excessive production in the body or introduction into the organism of toxins so that the balance between synthesis and conjugation on the one hand and toxin accumulation on the other is upset, will result in a severe injury to the gastro-intestinal mucosa. In this respect the hemicelluloses and pectins have a nutritive value that is clearly not caloric.

In conclusion it may be said that galacturonic acid plays a role similar to that of glucuronic acid in the detoxication mechanism. Furthermore, sugar acids from preformed sources are of greater value to the organism than those produced by synthesis. Sugar acids from preformed sources are therefore definitely sparing in their function while those produced by synthesis in the body represent a sacrifice of body protein and other essential precursors. It is obvious that such a sacrifice is self-limited. Foods containing hemicellulose and pectin, therefore, have a value separate and distinct from caloric considerations. From the nutritional standpoint, it seems desirable to modify the meaning of the term *unavailable* carbohydrate.

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Phenolphthalein Studies*
IV. Phenolphthalein Solubilities†

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AS "substances do not act unless they are soluble and in solution," the solubility of medicinal substances is of great importance: not only from the standpoint of administration of the medicament to the patient, but also from the standpoint of an understanding of the laws underlying the action of such substances upon living things.

WATER SOLUBILITY

We find that phenolphthalein is soluble at 25° C. in distilled water merely to the extent of 0.3 mgm.-% or 1:333,333, and that it retains this solubility at all degrees of pH-ion concentration from 1.1 up to 8.2. It may well be questioned whether phenolphthalein in this dilution has any biologic effects and experiments are in progress to answer this question.

In order to get more of phenolphthalein into aqueous solution, one may proceed in various ways: one may raise the hydrogen-ion concentration. Crystalline phenolphthalein dissolves at:

pH	*Solubility*
8.8	0.6 mgm.-%
9.0	1.1 mgm.-%
9.2	1.7 mgm.-%
10.0	14.0 mgm.-%

Curve 1 (Graph 1) shows this relation.

Obviously the soluble sodium phenolphthalein is not formed to any extent from the crystalline phenolphthalein at room temperature until the critical point of pH 9.0 is exceeded.

The following method was employed in the determination of solubility: 25 c.c. of buffer solutions of various degrees of hydrogen-ion concentration were saturated with excess of phenolphthalein by means of prolonged agitation in a shaking machine for several (usually three) hours. The solution was then filtered through a hard filter (Whatman No. 50) and the filtrate estimated for phenolphthalein: using equal volumes of filtrate and N/10 NaOH V.S. for the determination. For comparison we used a standard solution consisting of the same volume of N/10 NaOH and corresponding buffer solution, to which was added a 0.01% phenolphthalein solution to the point of color equality.

In view of the fact that the laxative action of phenolphthalein occurs at body temperature and the influence of temperature on the solubility of phenolphthalein might be of importance, we repeated the study with the buffer solutions of different pH values at a temperature between 38° and 40° C. by keeping them in a constant temperature bath and with occasional agitation after excess of phenolphthalein had been added. Curve 2 (Graph 1) demonstrates the difference, which is very slight (0.6 mgm.-%).

From this it will be seen that crystalline phenolphthalein is only slightly more soluble at body temperature; and it may well be questioned whether a solution of phenolphthalein as dilute as 6 per million has much effect upon living tissue.

"WATER SOLUBILITY" OF COLLOIDAL PHENOLPHTHALEIN

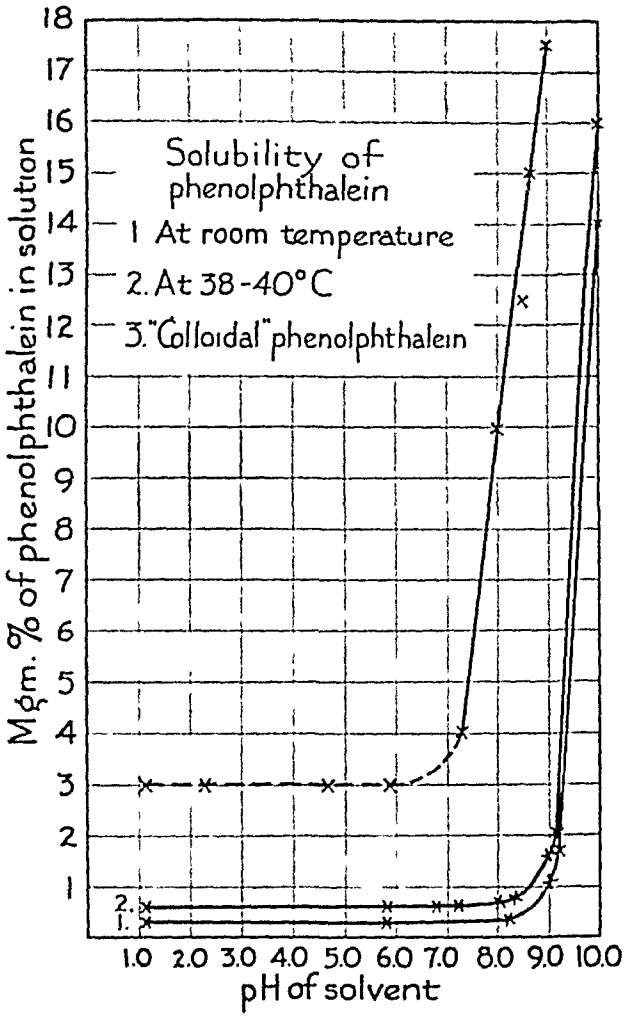
We are therefore faced by a mystery that might possibly be cleared up by the fact that a slightly soluble substance is the more soluble, the greater a surface it presents to the solvent. This raised the question whether there might not be a "colloidal" phenolphthalein of a much higher solubility rate, that might be produced in the bowel, to account for the cathartic action.

We have prepared colloidal phenolphthalein (1) by adding protective colloid (gelatin) to phenolphthalein, freshly precipitated in colloidal form, and find that the solubility of colloidal phenolphthalein is much greater than that of the crystalline variety. This is shown by line 3 (Graph 1) which was obtained in a manner somewhat different from the one that was used in developing curves 1 and 2 (Graph 1). The different procedure was necessary because of the impossibility of filtering the colloidal solution. We therefore estimated the amount of dissolved phenolphthalein by a direct matching of color as compared with an alcoholic standard solution of phenolphthalein added to fluid of the same pH-ion concentration. The broken portion of line 3 indicates that below pH 8.0 there is practically no color. Diffusion experiments (the results of which are represented by the broken line) indicate that a considerably greater amount of colloidal phenolphthalein is in solution than in case of the crystalline form.

The water solubility of phenolphthalein is also raised to a high degree when we add to water drop by drop a dilute (1%) solution of phenolphthalein in alcohol, as is practiced in the use of this substance as an indicator. This process gives the solubility and color reactions we consider characteristic for colloidal phenolphthalein, *i.e.* it strikes a pink color with a solution of sodium bicarbonate at pH 8.0. That we actually have to deal with colloidal phenolphthalein is shown by the fact that, after addition of a few drops of a 1% alcoholic solution of phenolphthalein to water, the pink reaction with sodium bicarbonate solution disappears after standing for a day or two. This is somewhat longer than is the case with colloidal phenolphthalein prepared by saturating a sodium phenol-

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Graph 1.

phthalein solution with CO_2. Perhaps this is because it is in neutral solution without the presence of an ionized salt, which would tend to "salt out" the colloid.

On prolonged (5 days') shaking of phenolphthalein with water (with aid of shaking machine), one secures an opalescent fluid that is richer in phenolphthalein, containing 0.00054 Gm. per 100 c.c.. This fluid cannot be cleared by filtration unless one repeats the filtration many times. That this is merely a fine suspension of microcrystalline and not colloidal phenolphthalein is shown by the fact that it does not give the pink color with sodium bicarbonate. That prolonged shaking has not actually increased the solubility of the phenolphthalein in water is furthermore shown by the fact that it is possible, if one returns the filtrate to the filter often enough to clear the solution; and then the fluid does not contain more than 0.3 mg.-%.

ALCOHOL SOLUBILITY

The solubility of phenolphthalein in alcohol at varying strengths is given in Table I and illustrated by Graph 2.

We see from these that the phenolphthalein solubility increases steadily until we reach a level exceeding 90 per cent by volume; from that point it decreases so that phenolphthalein is less soluble in absolute alcohol than it is in alcohol of official strength. The method employed in these determinations was that recommended by the United States Pharmacopoeia (2).

ALIPHATIC SERIES SOLVENTS

The solubility of phenolphthalein in other fluids of the aliphatic series besides alcohol is given in Table II, from which it will be seen that acetone is approximately three times better a solvent than is alcohol.

This observation seemed to merit special determinations of solubility in acetone-water mixtures of various strengths, which are given in Table III and shown in Graph 3. Here again, as in the case of alcohol, maximum solvent power is reached at 90 per cent, with a curious lessening in higher strength.

While our determination of alcohol solubility agrees with the U.S.P. figure, which is given at 1 Gm. in 12 (total of 13 c.c. of saturated solution containing 1 Gm. of phenolphthalein as shown in Table I), the figure for ether solubility which is given at 1 Gm. in 70 is one that we can not duplicate. We find it more nearly 1 Gm. in 100 (Table II). The slight solubility of phenolphthalein in chloroform and carbon tetrachloride is rather interesting. It is also remarkable that petroleum benzin and liquid petrolatum dissolve only 0.5 mgm.-%—not much more than does water.

AROMATIC SERIES SOLVENTS

The solvents of the aromatic series are rather low in potency, although the least efficient of those we studied —xylene—is five times a better solvent than water, which accounts for the fact that when xylene is employed for the preservation of urine, practically all of the phenolphthalein is found in the xylene layer.

OIL SOLUBILITY

The literature regarding the solubility of phenolphthalein in oils seems to be in an unsatisfactory condition, as well as methods for the determination thereof. After consultation with Dr. L. E. Warren, Senior Chemist, U. S. Department of Agriculture, we developed the following method:

A. Gravimetric method for determination of oil dissolved phenolphthalein. Place 5 c.c. of the saturated oil in a separatory funnel, add 20 c.c. of 0.1% solution of sodium hydroxide, separate the "soap" formed by the addition of 5 Gm. of sodium chloride. Transfer the alkaline solution containing the phenol-

Graph 2
Curve of Phenolphthalein Solubility in Alcohol of Various Concentrations

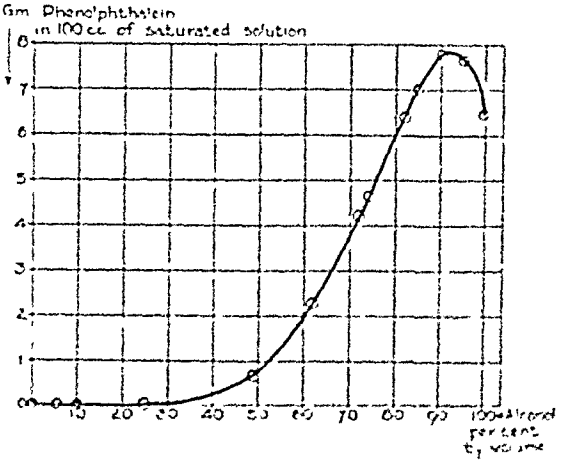


TABLE I

Solubility of phenolphthalein in alcohol-water mixtures of various strengths

ALCOHOL		PHENOLPHTHALEIN			
Specific Gravity at 15.56° C.	Per Cent by Volume	Specific Gravity of Saturated Solution at 25° C.	Grams per 100 Gm. of Saturated Solution	Grams per 100 c.c. of Saturated Solution	No. of c.c. of Saturated Solution that Contain 1.0 Gm. of Phtn.
0.79562	99.6	0.81860	7.91	6.474	15.45
0.81425	95.38	0.84063	9.12	7.668	13.04
0.8310	90.8	0.85415	9.046	7.725	12.95
0.8480	85.42	0.86814	8.102	7.035	14.22
0.8565	82.5	0.87638	7.325	6.42	15.58
0.87797	74.66	0.89195	5.23	4.668	21.42
0.8848	72.0	0.89365	4.76	4.253	23.04
0.90765	62.5	0.91068	2.56	2.33	42.91
0.9361	49.0	0.9376	0.763	0.715	140
0.97035	25.41	0.9746	0.0174	0.017	5882
0.98644	10.17	0.99086	0.0012	0.0012	83333
0.99264	5.12	0.99661	0.0006	0.0006	166666
1.0	0.00	1.00	0.0003	0.0003	333333

phthalein to another separatory funnel and continue the extraction of the phenolphthalein with 15 c.c. portions of 0.05% NaOH and 5 Gm. additions of NaCl until no more color can be extracted (four extractions usually suffice). To remove oil particles, treat the combined filtered alkaline solutions of phenolphthalein with 20 c.c. of petroleum ether, and discard the petroleum ether*; then acidify with hydrochloric acid and extract the phenolphthalein with ether, until a small portion of the original aqueous solution no longer gives a pink tint when made alkaline with NaOH.

Transfer the combined filtered ether portions to a

*Which can be done without appreciable loss owing to the slight phenolphthalein solubility in petroleum ether (Table II).

TABLE II

Phenolphthalein solubility in solvents arranged in order of potency

	Specific Gravity of Saturated Solution at 25° C.	Grams per 100 Gm. of Saturated Solution	Grams per 100 c.c. of Saturated Solution	Number of c.c. of Saturated Solution Containing 1.0 Gm. Phenolphthalein
A. Aliphatic Series				
Acetone	0.8886	5.32	21.1465	4.73
Ethyl Acetone	0.9087	5.20	4.728	21.15
Prophylene Glycol			3.50	
Ethylene Glycol			2.20	
Ether	0.7219	1.41	1.0185	98.18
Glacial Acetic Acid	1.048	0.191	0.200	500.0
Glycerin	1.252	0.052	0.065	1700.0
Carbon Disulphide	1.7773	0.026	0.047	2127.6
Chloroform	1.472	0.015	0.022	4545.0
Dilute Acetic Acid	1.007	0.007	0.007	14300.0
Carbon Tetrachloride	1.581	0.0013	0.002	50000.0
Kerosene	0.7943	0.0019	0.0015	66666.0
Petroleum Benzin	0.6345	0.0008	0.0005	200000.0
Liquid Petrolatum			0.0005	
B. Aromatic Series				
Benzene	0.8727	0.0046	0.004	25000.0
Toluene	0.8622	0.0029	0.0025	40000.0
Xylene	0.8573	0.0017	0.0015	66666.0

TABLE III

Solubility of phenolphthalein in acetone-water mixtures of various strengths

Specific Gravity at 25.0° C.	Per cent by Volume	Specific Gravity of Saturated Solution at 25° C.	Grams per 100 Gm. of Saturated Solution	Grams per 100 c.c. of Saturated Solution	Number of c.c. of Saturated Solution Containing 1.0 Gm. Phtn.
0.7887	100	0.8886	23.93	21.27	4.7
	95				
0.8284	90	0.9541	31.73	30.27	3.3
0.8570	80	0.9624	28.53	27.46	3.64
0.8712	75	0.9627	25.36	24.42	4.1
0.8860	70	0.9361	20.35	19.46	5.14
0.9091	60	0.9196	12.08	11.47	8.71
0.9293	50	0.9175	4.93	4.67	21.41
0.9702	25	0.9757	0.0266	0.026	3846.0
0.9870	10	0.9924	0.002	0.002	50000.0
0.9923	5	0.9985	0.001	0.001	100000.0
1.00	0	1.00	0.0003	0.0003	333333.3

tared weighing bottle, evaporate the ether and dry to constant weight. Since a small portion of the oil is carried through the process of extraction, a 5 c.c. portion of the oil used as the solvent is treated in exactly the same way (blank determination). The difference in weight of the two determinations represents the amount of phenolphthalein in 5 c.c. of the oil.

B. Colorimetric method for determination of phenolphthalein in oils. Since the procedure in the gravimetric method for the determination of phenolphthalein in oils is rather involved, and a check on results was desired, a colorimetric method was considered. Four colorimetric procedures were used, the final selection of the method depending upon the solubility of the oil.

Method B-1. Olive oil. Measure accurately 5 c.c. of oil saturated with phenolphthalein into a 100 c.c. glass cylinder; add 70 c.c. of ether and 25 c.c. of alcoholic KOH N 200. At the same time prepare a standard for comparison consisting of 5 c.c. of the same kind of oil used to dissolve the phenolphthalein, 70 c.c. of ether, and 25 c.c. of alcoholic KOH N/200. With a pipette graduated in hundredths of a c.c., add to this a standard solution of phenolphthalein (0.100 Gm. per 100 c.c.) until color equality, final reading being made with the aid of a colorimeter. From the amount of phenolphthalein required to produce the same color, the weight of phenolphthalein dissolved in the oil is calculated.

For expressed oil of almond, use 10 c.c. N 10 KOH instead of N 200 KOH. Otherwise proceed as above.

Method B-2. For oils practically insoluble in alcohol: cod liver oil, cotton seed oil, liquid petrolatum, or corn oil. Extract 5 c.c. of phenolphthalein saturated oil, measured accurately, with 25 c.c. portions of alcohol until the phenolphthalein is dissolved out, as shown by the fact that no color is obtained with alkali (three extractions usually suffice). Filter the alcoholic solutions through a hard filter. Prepare standard at the same time by extracting 5 c.c. of the same kind of oil used for solubility determination, to the same volume, with alcohol. Add 10 c.c. of alcoholic N/10 KOH to each cylinder and alcoholic standard phenolphthalein solution (0.100 Gm. per 100 c.c.) until color equality. Final reading with aid of colorimeter. Calculate.

Method B-3. For oils soluble in alcohol, such as castor oil. Add 5 c.c. of oil accurately measured to a 100 c.c. glass cylinder; add 85 c.c. of alcohol and 10 c.c. of alcoholic N/10 KOH V.S. Standard consists of 5 c.c. of same kind of oil used for determination, 85 c.c. of alcohol and 10 c.c. of the alcoholic N/10 KOH, and standard phenolphthalein solution (0.100 Gm. per 100 c.c.) measured accurately, to color equality.

Method B-4. Cod liver oil, etc. Place 5 c.c. of the saturated oil in a separatory funnel; add 20 c.c. of a 0.1% solution of sodium hydroxide, separate the "soap" formed by the addition of 5 Gm. of sodium chloride. Filter the solution and collect the filtrate in a 100 c.c. graduated glass cylinder. Continue the extraction of the oil with 15 c.c. portions of 0.05% NaOH and 5 Gm. additions of NaCl until the phenolphthalein is completely extracted. At the same time run a "blank" determination to be used as a standard for comparison, consisting of 5 c.c. of the same oil used for the solubility determination, extracting with exactly the same amounts of NaOH and using the same amount of NaCl. Make both solutions up to the same volume and add a standard phenolphthalein solution (0.100 Gm. per 100 c.c.) to the "blank" until color equality. Calculate amount of phenolphthalein in the oil.

In all of the colorimetric determinations, the reading of color should be made as quickly as possible, as a change in color may result.

Method of Saturating Oils with Phenolphthalein. To determine the solubility of phenolphthalein in oils, we saturate oil with phenolphthalein (1.0 Gm. per 100 c.c. oil) at room temperature (20-28° C.) for several days with occasional agitation, then in constant temperature bath at 25° C. for three hours with constant agitation. Filter at a temperature as near 25° C. as possible. Talc is used to facilitate clear filtering of the oils which did not filter clear.

The results are shown in Table IV, from which it will be seen that castor oil is by far the best among the oily solvents: dissolving ½ Gm. per 100 c.c.. All the other oils tested are poor solvents with relatively little difference among them. Liquid petrolatum, which is not of course a true oil, is as was previously mentioned the poorest solvent of them all. It will be seen from Table IV, that the alcohol solubility of the oils is

TABLE IV

Solubility of phenolphthalein in oils

	Grams of Phthn. Dissolved by 100 c.c.	Alcohol Solubility of Oil
Castor Oil	0.500	miscible
Cod Liver Oil, dark amber	0.032	0.325
Cotton Seed Oil	0.022	0.0878
Expressed Oil Almond	0.020	0.0628
Corn Oil	0.019	0.0566
Cod Liver Oil, light amber	0.016	0.1612
Olive Oil	0.014	0.071
Liquid Petrolatum	0.0035	0.011

not proportionate to their ability to dissolve phenolphthalein; hence is of no value in explaining the difference in the solvent power of the oils.

That alcohol solubility may be of some significance however is shown in our experience with two different kinds of cod liver oil, given in Table IV.

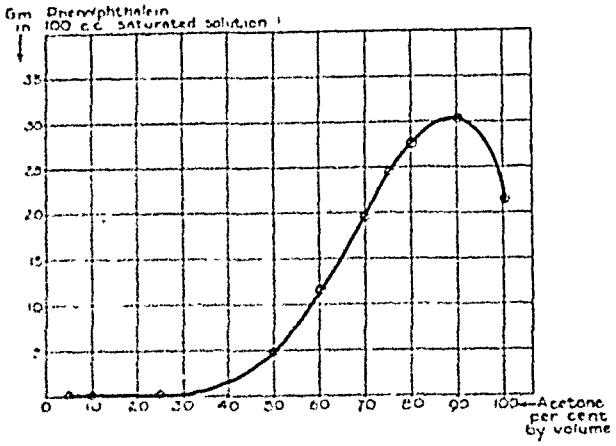
	Gm. of Phthn. Dissolved by 100 c.c.	Alcohol Solubility in cil	Saponification Value
Cod liver oil, dark amber	0.032	0.3250	210.5
Cod liver oil, light amber	0.016	0.1612	184.6

The fact that the dark amber cod liver oil dissolved twice as much phenolphthalein as the light amber and that it is also twice as alcohol-soluble as the light may possibly be significant. The saponification value shows no proportionate relation.

CONCLUSIONS

1. Phenolphthalein is almost insoluble in water or buffer solutions up to pH 9.0, even at body temperature.
2. Colloidal phenolphthalein is considerably more soluble and at a lower hydrogen-ion concentration, being capable of producing the pink sodium phenolphthalein with $NaHCO_3$ solution of pH 8.0-8.2.
3. The solubility in alcohol increases with increase in strength of alcohol water mixtures up to that of the U.S.P. official alcohol. It is slightly less in absolute alcohol.
4. The liquids of the aliphatic series are in general better solvents for phenolphthalein than are those of the aromatic series. Notable exceptions to this proposition are carbon tetrachloride and the petroleum products which are very poor solvents.
5. Phenolphthalein is, in general, but poorly dissolved by oil with the exception of castor oil, which is capable of dissolving as much as ½% of phenolphthalein.

Graph 3
Curve of Phenolphthalein Solubility in Acetone of Various Concentrations



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Bile Salt Therapy in Liver and Gall Bladder Disease*

By

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WHENEVER the management of a case of liver or gall bladder disease is undertaken one must balance the prospects of satisfactory results from surgical treatment against those to be expected from a carefully conducted medical regime.

There is abundant literature regarding the results of gall bladder surgery and there is for the most part little discrepancy in the findings. Judd (1), in analyzing the results of cholecystectomy upon the basis of pathologic changes in the gall bladder, found that when these changes were minimal the results were satisfactory in 64 per cent of the cases, and when cholecystitis and stones were found they were satisfactory in 87.8 per cent. However, in cases of noncalculous cholecystitis, Graham and Mackey (2) reported satisfactory results in only 30 per cent of the cases and improvement in another 30 per cent in which cholecystectomy had been done.

It is evident from these reports as well as from the results of other investigators that only in the presence of severe symptoms (such as colic) associated with gall stones will removal of the gall bladder give satisfac-

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tory results in a large percentage of the cases. Even in many of these, subsequent investigation will reveal that, although entirely relieved from pain, these patients continue to suffer from indigestion, food intolerance, and constipation.

Unfortunately reports of the follow-up studies of large groups of gall bladder cases treated medically are extremely rare. Blackford, King and Sherwood (3) recently reported a group of 200 unoperated cases of gall bladder disease. Based upon an eight year follow-up period they found that 37 per cent of the patients with proved cholecystitis were living and had been relieved to a satisfactory extent by a plan of treatment which included careful restriction of diet, removal of foci of infection, and the use of mild saline cathartics.

The employment of cholagogic drugs in the treatment of liver and gall bladder disease has always been regarded as a very valuable and logical approach to the medical treatment of these cases. In a theoretical consideration of the metabolism of the bile acids (4), one finds many factors which support the rationale of their use in the medical management of gall bladder disease.

It is a well known fact that the bile acids are manufactured in the liver from protein substances in the food and from protein decomposition products produced by the breakdown of the body tissues. Whipple and his co-workers (5) have shown that tryptophane is the most important precursor of the bile acids.

The functions of the bile acids after they reach the intestinal tract are well known. They aid in the digestion and absorption of the fats; they have been shown to stimulate the flow of pancreatic enzymes; they seem to have a tonic effect upon the intestinal motility.

A unique feature of the metabolism of the bile acids is the manner in which a fraction of the total bile acid secreted is reabsorbed from the intestine and carried back to the liver. Within the liver the bile acids are thought to act as the chief stimulant to the hepatic cells in causing the production of additional quantities of the bile acids. However, at the present time little is known of the intra-hepatic regulatory mechanism which controls the secretion or destruction of the bile salts within the liver.

Another important rôle ascribed to the bile acids by both Wright and Whipple (5), and Andrews and his associates (6) is the relation of the bile acids to the metabolism of cholesterol. It has been shown that cholesterol tends to precipitate out of the bile in which the bile acid content has been reduced. Many see in this phenomenon a possible explanation for the formation of gall stones. Further studies have shown that infections of the biliary tract may cause a reabsorption of the bile salts from the gall bladder thus reducing their concentration in the bile and thereby influencing the precipitation of cholesterol. Infections in other parts of the body and pregnancy have also been shown to have a similar effect upon the bile acid concentration. Thus it may eventually be found that the bile salt—cholesterol ratio is a very important factor in the etiology of cholelithiasis.

In reviewing the accepted plans of medical treatment of gall bladder disease it is apparent that, although most writers mention the use of bile salt preparations, bile salt therapy has not been very successful in this country, and only a few detailed studies are available. The explanation of this lack of success is that the preparations used have consisted of the least active and the most toxic of the bile salts. For this reason the dosage has been too small to produce any real benefits, and it has been necessary to fortify most preparations with cathartics in order to produce any demonstrable effect upon the constipation which commonly occurs in this group of patients. Neubauer (7) has shown that dehydrocholic (desoxycholic) acid has the strongest cholagogic and choleretic activity of any of the bile acids and is at the same time the least toxic. A few German (7) and American clinicians (8) have given dehydrocholic acid and its sodium salt considerable trial, but the use of the more effective forms of bile salts without fortification with other drugs has been generally neglected. In view of these facts we have attempted to test the clinical value of a bile salt preparation† containing a high percentage of desoxycholic acid.

Patients were referred for this study from the General Medicine Clinic of the Indianapolis City Hospital and were treated for the most part as out-patients. All patients were placed on the same diet, one in which there was a definite fat restriction with moderate carbohydrate and high protein content. Coöperation concerning diet was poor inasmuch as many of the dispensary patients were either on relief or on strictly limited incomes. A number of apparent failures and recurrences could be definitely ascribed to dietary indiscretion. Fifteen patients seen in private practice are included in this group, and in these cases better coöperation is reflected in more satisfactory response to treatment.

The bile salt preparation was administered in 5 grain capsules. These were given before or during meals. Patients were started on one capsule three times daily, and the dose was increased until regular bowel movements were obtained without taking any cathartics. One patient required 75 grains a day for several days before the bowels began to move. No untoward symptoms developed and the dose was gradually reduced. Most patients found the optimum dose to be two to three capsules three times daily. A number of patients complained that the stools were quite loose and that there was some abdominal pain at first. In most instances this quickly disappeared, and the patients stated that the bowels moved regularly once or twice daily, usually soon after meals, and that the stools were soft, formed, and very dark in color. In several cases the benefits of this treatment seemed to be enhanced by the addition of tincture of belladonna in the usual doses.

RESULTS

A group of 63 patients was treated with bile salts over a period of nine months. For purposes of discussion we have divided these cases into three divisions.

The first group is composed of 22 cases of cholelithiasis. In these patients gall stones were definitely demonstrated either by X-ray study or palpation at time of surgery or by finding cholesterol crystals in the bile of patients with a nonvisualizing gall bladder. Frequent attacks of colic, intolerance to fat or fried foods, and chronic constipation with flatulance were

†Bilron (Iron Bile Salts, Lilly) supplied through the courtesy of Eli Lilly and Company.

characteristic findings which occurred in all of these cases.

The results obtained in this type of patient by the method of treatment as previously outlined are shown in Table I. It is evident that in the majority of cases pain was not satisfactorily removed by this medical treatment. However, better results were obtained in relief of constipation and digestive symptoms. In all patients with definitely proved cholelithiasis who were

TABLE I

Results of treatment in 22 cases of proved cholelithiasis

	Relieved	Improved	Unimproved
Pain	10	2	10
Food intolerance and indigestion	11	6	3
Constipation	15	4	1

Résumé of clinical findings:
Jaundice in 11 cases
Typical attacks of colic in 22 cases
Gastro-intestinal disturbances in 20 cases
Cholecystograms—positive (shadow of stones seen) in 13 cases
—negative, plus cholesterol crystals in bile in 2 cases

suitable surgical risks we have recommended surgery. Seven of these patients have been operated on at the present time.

The second group is composed of 16 patients with cholecystitis without proof of the presence of stones. In all of these patients attacks of colic, digestive disturbances with food intolerance, and constipation had occurred, but X-ray findings and laboratory studies did not offer definite proof of the presence of gall stones. The results are given in Table II. The treatment was more successful in these patients. Pain was entirely relieved in a large proportion of them, and the marked improvement of digestive symptoms in all was most striking. These results compare satisfactorily with those obtained in this type of patient with surgical treatment.

The third group is made up of 25 patients with symptoms indicative of gall bladder dysfunction but in whom positive evidence of actual disease of the gall bladder may be lacking. It is difficult to definitely classify all of these patients. In some, indigestion and constipation of the type ascribed to hepatic insufficiency may be the only evidence of pathology. Pain is very indefinite or may be completely absent. True colic with subscapular radiation does not occur. The stools are characteristically light yellow. Headaches, vertigo, nausea and vomiting are the symptoms which complete this syndrome. The mechanism which is capable of producing this syndrome is not known at the present time, but it is apparent that there is some relation to hepatic insufficiency, although it may be impossible to demonstrate this hepatic failure by any of the ordinary liver function tests.

TABLE II

Results of treatment in 16 cases of cholecystitis in which the presence of gall stones could not be proved

	Entirely Free	Improved	Unimproved
Pain	5	8	3
Constipation	11	2	
Indigestion	6	10	

Résumé of clinical findings:
Jaundice in 4 cases
Attacks of colic in 7 cases
Gastro-intestinal disturbances in all cases
Cholecystograms—nonvisualized in 11 cases
—faintly visualized with *failure to empty in 20 hours* in 5 cases

Very satisfactory results were obtained in this group (Table III). Furthermore, when bile salts were discontinued temporarily in these patients, all symptoms returned and similar results could not be obtained by means of dietary control alone or by means of cathartics.

In this group of patients we would frequently find "gall bladder disease" given as the diagnosis, but without definite pathology to be found in the gall bladder at surgery. As the experience of most physicians will

TABLE III

Results of treatment in a miscellaneous group of 25 cases of functional biliary and hepatic disturbances

		Entirely Free	Improved	Unimproved
Pain	Definite (14 cases)	8	4	2
	Indefinite (6 cases)	6	—	—
Indigestion		22	2	1
Constipation		22	2	1

Résumé of clinical findings:
Jaundice absent in all cases
Attacks of colic absent in all cases
Pain { definite upper right quadrant in 14 cases; vague, generalized abdominal pain in 6 cases; no history of any pain in 5 cases
Cholecystograms { normal in 10 cases; failed to visualize or faintly visualized in 12 cases

bear out, surgery will not alleviate these symptoms, and it is in these patients also that we find the largest proportion of recurrence of symptoms postoperatively.

CONCLUSIONS

1. Results of surgical treatment of patients with symptoms of biliary tract disease, but who do not have gall stones or attacks of biliary colic, are frequently unsatisfactory.

2. In this series of cases marked benefits were obtained by a plan of medical treatment consisting of a low fat diet and the administration of a pure bile salt preparation having high concentration of desoxycholic acid. The most marked improvement was seen in the control of digestive symptoms and constipation.

3. Less satisfactory results were obtained in patients with cholelithiasis than in the noncalculous cholecystitis group. The best results occurred in the miscellaneous group consisting of persons with hepatic insufficiency, biliary dyskinesia, and other functional disorders of the liver in which the secretory mechanism seemed to be sluggish.

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SECTION VII—*Surgery of the Lower Colon and Rectum*

Clinical and Therapeutic Status of Cases of Colonic Diverticulosis Seen in Office Practice*

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AN analysis has been made of 72 cases of diverticulosis found in a survey of the authors' office records. Patients seen initially in the hospital and *home have been purposely excluded in order to present* a statistical study of office material. This type of study should give a more accurate idea of the incidence of the abnormality, frequency of symptoms and of complications than previously reported series of cases collected from both ambulant and hospital sources. It *is the nearest approach to a survey of a cross section* of the population who do not seek medical aid.

Incidence. Thirty-eight of these cases were found in making a study of 463 consecutive cases upon whom barium enemas were carried out, giving an incidence of 8.2 per cent. These figures approximate those of Ochsner and Bargen, who found colonic diverticula in 7 per cent of 2,747 patients examined roentgenologically, and those of Spriggs and Marxer, who reported diverticula or pre-diverticulosis in 100 of 1,000 patients examined.

A comparison is made between functional colopathies and diverticulosis (Fig. 1). Fifty-three per cent of our office cases showed some type of functional colonic abnormality, whereas diverticula occurred in the colon in only 8.2 per cent. This tends to refute any argument which might be advanced that diverticula are more prone to develop in colons which are the seat of a neuromuscular irritability. A racial factor is of interest in this connection. Thirty per cent of the patients with functional abnormalities, largely "irritable" colon, were Jewish while only 13 per cent of those with diverticulosis were of this race.

Age and Sex. The age distribution of these two groups of office patients are shown graphically in Figure 1. The number of patients encountered with the so-called "irritable" colon diminishes gradually after age 35, whereas there is a steady increase in diverticulosis after this age. Seventy-two per cent of the latter were over 50 years of age, the average age of the group being 55.4 years. The youngest patient was thirty and the oldest 81 years of age. These figures simulate those of Ochsner and Bargen and of Spriggs and Marxer. There were no patients under 30 years of age in either of these two series. There was practically no difference in the sex distribution of our cases, 34 were male and 38 female. The age averaged the same in the two sexes.

Constitutional Habitus and Obesity. In this group 43 patients were classified as normal or sthenic habitus, 12 hypersthenic and 17 asthenic. There seems to be no predilection for any particular habitus, although the incidence of diverticulosis in those of asthenic build (23.6 per cent) is somewhat less than the occurrence of this habitus in office patients. Some credence has been given to the theory that obesity may encourage the development of colonic diverticula. Thirty-three patients, or 46 per cent, of the group either were obese (21) or had been overweight in the

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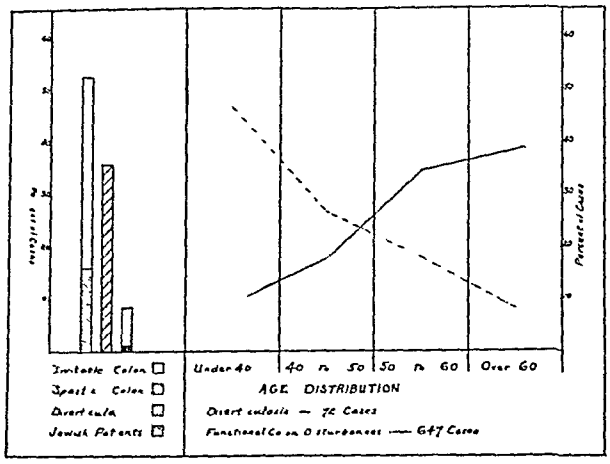


Fig. 1. Comparison of incidence (occurrence in Jewish patients) and age distribution of cases of "irritable" colon with cases of diverticulosis.

past. This incidence of obesity is somewhat higher than expectancy in office cases

Bowel Habit. Many writers have stressed the importance of constipation as a predisposing factor in the development of colonic diverticula The data relating to previous habits of defecation in this group are significant as particular attention was devoted to this question in the taking of the histories. Hospital records are frequently incomplete in this regard. It was found that only 32 patients or 44 per cent had been chronically constipated, 29 per cent of these having had the condition for more than 10 years. Ten of the group with constipation had had attacks of diarrhea. Twenty-nine patients or 41 per cent of the cases

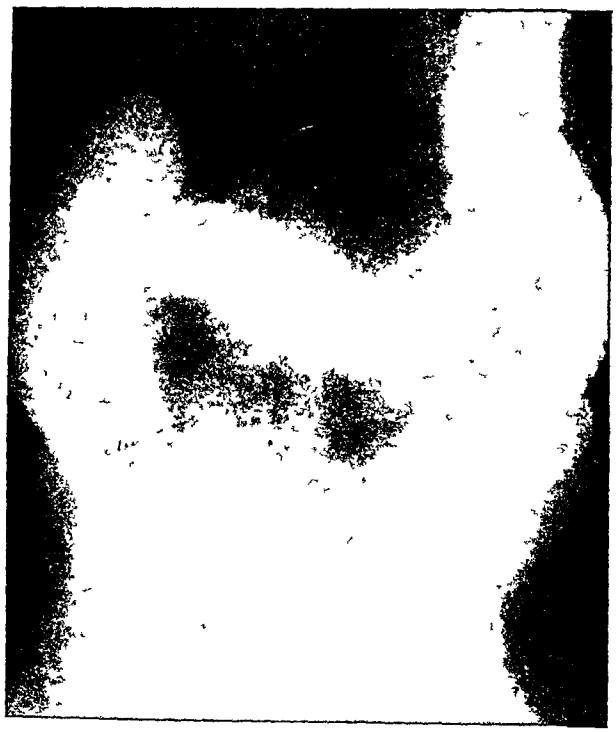


Fig. 2. Showing a few diverticula in the descending and pelvic segments protruding from the outline of the completely filled colon.



Fig. 3. Same patient as Fig. 2 showing innumerable diverticula scattered throughout the descending colon after evacuation of the barium enema.

gave a history of normal bowel habit, ten of whom occasionally complained of diarrhea. A persistent tendency toward diarrhea alone was noted in 11 patients or 15 per cent of the entire series. This incidence of constipation in the entire group is less than



Fig. 4. Showing sizeable filling defect in patient with a palpable tumor following an attack of diverticulitis.

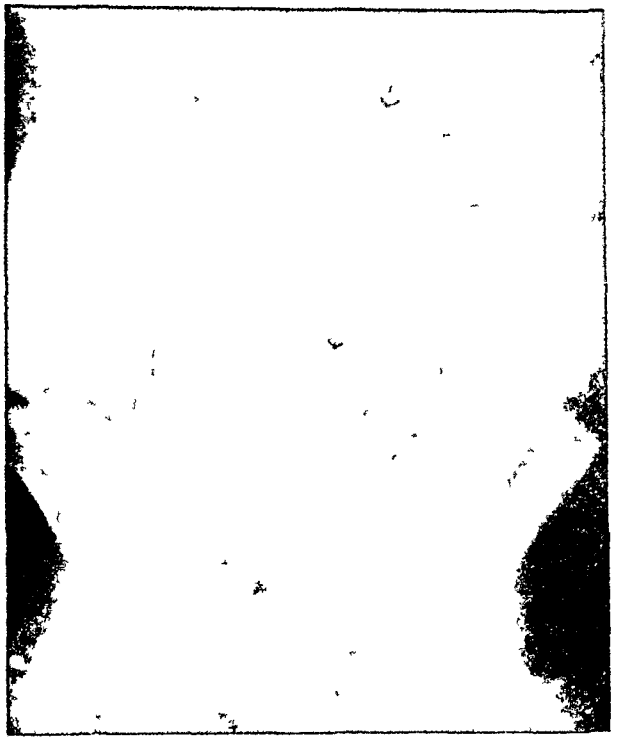


Fig. 5. Triangular incisura-like defect in pelvic and transverse segments of colon in patient with history of several severe attacks of diverticulitis simulating partial obstruction.



Fig. 6. Illustrating the deep incisura like defect in the pelvic colon in a patient with history of attacks of diverticulitis.

that for admissions to the office for all causes (56 per cent). The occurrence of constipation in our practice does not steadily increase with age as does the age distribution of diverticulosis. Therefore, it seems doubtful if constipation per se is an important predisposing cause of diverticulosis. We have seen diverticulosis in a number of patients, who gave a history suggestive of an active gastrocolic reflex, *i.e.*, a life-long tendency to defecate after meals or excitement.

Diagnosis. Ochsner and Bargen report finding diverticular sacculation, fixation of the sigmoid or actual diverticula in 15 of 72 patients subjected to sigmoidoscopy. A positive sigmoidoscopic diagnosis can only be made by actually visualizing the diverticula, and the above mentioned authors did not specifically record this finding in their cases. We failed to

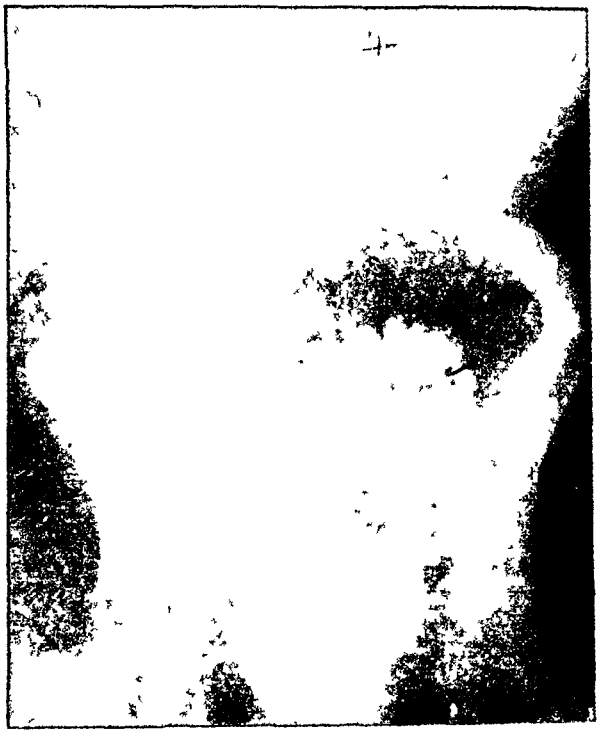


Fig. 7. Suggestion of same appearance in the pelvic colon. There is a diverticulum projecting from both sides of the deep incisura like defects.

demonstrate a diverticulum in 46 patients who were examined, and we have actually seen but one diverticulum through the sigmoidoscope in the past 10 years. The failure to see the pouches sigmoidoscopically is due primarily to their location above the reach of the ordinary 10 inch sigmoidoscope. In some instances it may be due to difficulty in distending the upper sigmoid because of spasm, and in others to sharp angulation and deep mucosal folds. The diagnosis must depend primarily upon the roentgenological examination of the colon. The technique of methods of demonstration of diverticula has been well presented by Case and Spriggs and Marxer and need not be dwelled upon here. Figs. 2 and 3 illustrate the superiority of the film taken after evacuation of the opaque enema as compared with the "filled colon" film. Diverticula are frequently completely obscured by complete filling of the colon with barium.

TABLE I
Chief complaints

Diarrhea		18
Constipation		13
Epigastric Pain or Distress		12
Flatulence		9
Duodenal Ulcer Syndrome		9
Lower Left Quadrant Pain		5
General Abdominal Distress)	(3)	
General Abdominal Pain)	(4)	7
Lower Abdominal Pain		5
Upper Left Quadrant Pain		4
Dizziness		3
Headache		3
Nausea		3
Bloody Stools		3
Melena		2
Upper Right Quadrant Pain		2
Lower Right Quadrant Pain		1
Asthma		1
Angio-neurotic Edema		1
Chest Pain		1
Dysuria		1
Hematuria		1

TABLE II
Diagnoses

Colon Stasis	15
Diverticulitis	14
Diverticulosis	7
Duodenal Ulcer) Diverticulosis)	9
Duodenal Ulcer	2
"Spastic" or "Irritable" Colon) Diverticulosis)	7
Gastro-duodenitis	3
Diverticulosis) Colon Stasis)	2
Gall Bladder Disease) Diverticulosis)	4
Rectal or Sigmoidal Polyp) Diverticulitis)	2
Diverticulosis) Polyp)	1
Carcinoma of Stomach	2
Pyelitis	1
Primary Pernicious Anemia	1
Hiatus Hernia	1
Hypertension	1

TABLE III

	LOCATION	
Pelvic Colon	28 Cases	39 per cent
Left Half of Colon or Less	34 Cases	47 per cent
Entire Colon	4 Cases	5 5 per cent
Ascending Colon	3 Cases	4. per cent
Right Half of Colon	1 Case	1 5 per cent
Transverse Colon	1 Case	1 5 per cent
Rectum	1 Case	1 5 per cent
	SIZE	
Small	50 Cases	69 5 per cent
Moderate	15 Cases	21 per cent
Large	7 Cases	9 5 per cent
	NUMBER	
Many	22 Cases	30 5 per cent
Few	50 Cases	69 5 per cent

Other Diverticula. Duodenal diverticula were demonstrated in 4 cases and suspected in 2 more. In all but one, a duodenal ulcer syndrome was present. A small diverticulum was seen in the terminal ileum in one case and suspected in 4 others. Small diverticula in the terminal ileum undoubtedly escape diagnosis in many instances.

Clinical Status. General recognition is accorded frank attacks of diverticulitis, but there exists a generally accepted belief that diverticulosis is very often asymptomatic. Spriggs and Marxer could find no symptoms referable to the condition in one-third of their cases. In many instances, it is exceedingly difficult to determine accurately the part played by the diverticula in the initiation of certain symptoms. Table I lists the chief complaints on admission in the order of their frequency. Diarrhea, heading the list with 18 patients (21 per cent), occurred more fre-

TABLE IV
Relationship of symptoms to number of diverticula

	Few Diverticula	
50 Cases	Symptoms in 27	54 per cent
Diarrhea	22 Cases	44 per cent
Diverticulitis	9 Cases	18 per cent
Bleeding	12 Cases	24 per cent
Gross	4 Cases	8 per cent
Occult	8 Cases	16 per cent
	Many Diverticula	
22 Cases	Symptoms in 12	54 5 per cent
Diarrhea	11 Cases	50 per cent
Diverticulitis	7 Cases	32 per cent
Bleeding (Gross)	1 Case	5 per cent

TABLE V
Relationship of symptoms to location of diverticula

Pelvic Only:	28 Cases	Symptoms in 16	57 per cent
Diarrhea	13 Cases	46 per cent	
Diverticulitis	3 Cases	10 per cent	
Bleeding	8 Cases	28 per cent	
Gross	2 Cases	7 per cent	
Occult	6 Cases	21 per cent	
Left Half or Distal	34 Cases	Symptoms in 19	56 per cent
Diarrhea	14 Cases	41 per cent	
Diverticulitis	10 Cases	29 per cent	
Bleeding	3 Cases	9 per cent	
Gross	3 Cases		
Occult	0 Cases		
Entire Colon.	4 Cases	Symptoms in 4	100 per cent
Diarrhea	3 Cases	75 per cent	
Diverticulitis	3 Cases	75 per cent	
Bleeding	0 Cases		
Miscellaneous: Ascending, Proximal ½, Transverse, Rectum			
	4 Cases	Symptoms in 2	
Diarrhea	1 Case		
Bleeding (Occult)	1 Case		

quently than in any series of cases reported previously. The percentage of patients with diarrhea either on admission or in the past was much higher (45 per cent). Excluding the emotional factor, no other cause for diarrhea was found except in four patients who had an achlorhydria. Constipation was the chief complaint in 13 cases, but in most instances it had been present more than 10 years and must have antedated the development of diverticula quite frequently. Other complaints which may have depended in some measure upon diverticulosis were flatulence occurring 9 times, abdominal pain and distress in various locations 24 times, and bloody stools 3 times. We feel confident that many bouts of slight abdominal distress and irregular bowel habit, often following the ingestion of large amounts of roughage or excessive physical exercise or long automobile rides, are dependent upon irritation of colonic diverticula. A careful history in many individuals with diverticulosis will reveal such attacks of varying severity in the past. They usually go undiagnosed unless a severe attack of diverticulitis develops. The same clinical picture in younger patients is more often dependent upon a so-called "irritable" or "unstable" colon. Excluding constipation, symptoms which may have depended upon diverticulosis in this series occurred in 54 cases or 75 per cent.

Another method of attempting to ascertain the clinical significance of diverticulosis in this series is afforded by an analysis of the chief diagnoses (Table II). It will be noted that diverticulosis or diverticulitis was entered as one of the major diagnoses in 46 cases or 64 per cent. Allowing for the personal equation, these data suggest that well over 50 per cent of patients with diverticulosis visiting the office of a gastro-enterologist have symptoms dependent upon this condition. It is highly probable that many of the remaining patients have had symptoms in the past attributable to slight irritation of diverticula.

Relationship of Symptoms to the Number, Location and Size of Diverticula. Table III denotes statistical data relating to location, size and number of diverticula which does not differ materially from similar statistics published elsewhere. By consulting Table IV, it will be noted that the incidence of symptoms collectively did not depend upon the number of diverticula found. However, the occurrence of symptoms thought to be due to diverticulitis was almost twice as great in the cases with many pouches as those with few. The incidence of bleeding was much greater in the group with few diverticula, but in some of these patients the bleeding was probably from some other source.

In Table V, the symptomatology in relation to the site of the diverticula is given. There was no essential difference in the incidence of symptoms occurring in cases with diverticula confined to the pelvic colon and those with pouches throughout the left colon. However, complaints which were attributed to diverticulitis occurred three times more often in patients with diverticula of the entire left colon as compared with those with pouches in the pelvic colon only. The few patients with involvement of the entire colon all presented symptoms thought to be due to the diverticula.

The incidence of pertinent symptoms increased steadily as the recorded size of the diverticula increased (Table VI). The occurrence of diarrhea, diverticulitis and bleeding was consistently greater in patients with large pouches than in those with smaller diverticula.

DIVERTICULITIS

In 16 cases or 22 per cent of the entire group attacks suggestive of diverticulitis had occurred in the past or appeared during observation. Ochsner and Bargen report a comparable incidence of diverticulitis in 27 per cent of cases. Twelve of our patients were men. The average age and age range was identical with the entire diverticulosis group. We have previously noted that the occurrence of "diverticulitis" symptoms is much greater in patients with many diverticula. Likewise the larger pouches seem more prone to be associated with symptoms of this type. Pain, the outstanding symptom in diverticulitis, occurred in 14 patients or 87.5 per cent. In all but three, the pain was located somewhere in the left or lower abdomen, most commonly in the lower left quadrant. Fever was associated with attacks in 6 cases (37 per cent), hematuria in 1 case and gross hemorrhage from the bowel in 1 case. Two cases were examples of the hyperplastic type, having a palpable tumor and symptoms of partial obstruction. Fig. 4 shows the roentgen defect in one of these cases when first seen two months after an attack of diverticulitis. The defect has gradually diminished in size during a period of observation of more than one year. The second case with a similar history has been followed for three months. Both have remained symptom-free, the stools have been persistently negative for occult blood and considerable weight gain has taken place. The tumor in both patients has become smaller, probably due to subsidence of the inflammatory reaction and absence of inspissated feces proximal to the partial obstruction. A differentiation from malignancy is frequently impossible in cases of this type, but diverticulitis is suggested by the "inflammatory" feel of the mass, the appearance of zonal spasm by X-ray without evidence of an actual encroaching defect, the absence of weight loss, rapid clearing up of symptoms and disappearance

TABLE VI

Relationship of symptoms to size of diverticula

Small:	50 Cases	Symptoms in 26	52 per cent
Diarrhea	20 Cases	40 per cent	
Diverticulitis	10 Cases	20 per cent	
Bleeding:	5 Cases	10 per cent	
Gross	2 Cases	4 per cent	
Occult	3 Cases	6 per cent	
Variable or Moderate:	15 Cases	Symptoms in 9	60 per cent
Diarrhea	7 Cases	49 per cent	
Diverticulitis	4 Cases	24 per cent	
Bleeding:	5 Cases	33 per cent	
Gross	3 Cases	27 per cent	
Occult	2 Cases	6 per cent	
Large:	7 Cases	Symptoms in 7	100 per cent
Diarrhea	6 Cases	86 per cent	
Diverticulitis	2 Cases	30 per cent	
Bleeding (Occult)	2 Cases	30 per cent	

of occult blood from the stools. The sigmoidoscope may help. Most cancers of the left colon are within reach of the sigmoidoscope, and there is only rarely sufficient spasm or edema below the growth to prevent its visualization. In diverticulitis causing trouble low down, the instrument comes on bowel lumen closed by edema and spasm and gives a sensation of fixation *without demonstrating a mass. The bowel habit in* these patients with diverticulitis was on the side of frequency, diarrhea was present in 10, constipation in 3 and the function was unchanged in 3 cases.

We should like to draw attention to a peculiar appearance of angulation and fixation of one border of the bowel silhouette without any appreciable distortion of the other margin which we have previously encountered in cases of diverticulosis and which we have not seen described. This wide triangular incisura was noted in 3 cases in this series, and all had had attacks of diverticulitis (Figs. 5, 6 and 7). We suspect that this roentgen finding may result from contraction of the bowel wall due to a small ciccatrix at the site of a previously inflamed diverticulum. It is probable that this type of defect may in some instances result from exceedingly deep irregular haustral contractions. The character of the defect is not unlike that seen on the greater curvature of the stomach opposite to a lesser curvature ulcer or in the duodenal cap in association with ulcer. We feel that regardless of the mechanism which may be responsible for its occurrence, its frequent association with diverticulitis is worthy of recording. Carcinoma of the colon rarely produces this appearance.

Bleeding. Too little attention has probably been given to diverticula as a cause of bleeding from the bowel in older individuals. In this entire series bleeding of some type occurred in 28 cases or 39 per cent. Melena in 3 instances was attributed to a demonstrable lesion of the stomach, duodenum or liver. In the remaining 8 cases of gross bleeding polypi were present in the rectum or sigmoid in three, leaving 5 cases or 7 per cent of the entire group without cause other than the diverticula. Occult blood was positive in the stools in 17 instances. Demonstrable gastro-duodenal lesions probably accounted for this finding in eight and hemorrhoids in one. There remains 8 cases or 11 per cent in which the diverticula may have been responsible. Ochsner and Bargen noted bleeding in 5 per cent of their cases of diverticulosis and in 22 per cent of the diverticulitis cases. There was no difference between the incidence in these two groups in our series. Bleeding occurred in 3 cases or 18 per cent in diverticulitis and in 10 cases or 18 per cent in diverticulosis. Obviously since diverticulosis is comparatively common in later life, it must constitute one of the more frequent causes of bowel bleeding in older patients.

Treatment. Bowel rest and attempt at correction of associated disturbance of normal bowel habit constitutes the principle of therapy. In the acute case without obstruction, the diet consisted of surgical liquids until all discomfort disappeared. It was then enlarged to include all foods except those with fibre, which seems to be badly borne in many instances. The addition of fiber to the diet must be made very slowly and cautiously. If bowel habit is on the "loose" side, caution is necessary in the use of very hot or cold foods and drinks. Lubricating oil by mouth and rectal instillations of olive oil or cotton seed oil are soothing, when tolerated. The medicinal management is that of the "irritable" colon, *i.e.*, sedative and antispasmodies, such as belladonna and calcium. A mixture of bismuth, barium sulphate and kaolin was used in practically every instance where inflammation was suspected without obstruction. The most important phase of therapy is the prevention of future attacks by attention to proper diet, violent exercise in some and neuroses and emotional upsets in others.

Prognosis. The prognosis of diverticulosis and uncomplicated diverticulitis is good. While many patients may have minor symptoms from time to time, major complications are rare. Twelve of our patients have been followed for 5 years or more and in no instance has a serious complication occurred. We encountered no instance of associated malignancy of the colon in this series. Ranken and Brown reported 4 cases of carcinoma in 227 cases of diverticulitis, which they believed to be entirely incidental. Ochsner and Bargen found malignancy of the colon in 6 per cent of 208 cases.

SUMMARY

A series of 72 consecutive cases of colonic diverticulosis encountered in office practice has been reviewed in order to ascertain the incidence of the abnormality and the frequency with which symptoms and complications are to be anticipated in the ambulant patient.

The study affords an interesting comparison with functional colonic disturbances in relation to age and race incidence.

Previous bowel habit of these patients has been carefully analyzed and reveals a lesser incidence of constipation than that ordinarily recorded. Diarrhea occurred in a surprisingly large number of our patients. Our statistics support the contention that diverticulosis produces symptoms from time to time in most cases. The relationship of symptoms to the number, location and size of the pouches is of interest, particularly in those with diverticulitis.

Cases with diverticulitis have been segregated and analyzed. Attention is drawn to a type of roentgen defect which may follow an attack of severe diverticulitis and which we have not seen described in the literature.

The review tends to establish the more frequent occurrence of bleeding from the bowel than is generally appreciated.

A follow-up in these office cases has indicated the rarity of severe complications and of concomitant carcinoma.

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Annual Abstracts of Proctologic Literature

(May, 1934-May, 1935) By CLEMENT L. MARTIN, M.D., Chicago, Illinois

The complete bibliography from which these Abstracts were made will be published in full in the Transactions of the American Proctologic Society, 1935.

INTRAPERITONEAL VACCINATION

Steinberg and Goldblatt (see 1934 Transactions) found that the injection of heat-killed *B. coli* suspended in a saline solution and injected into the abdominal cavity, decreased the incidence of peritonitis after operation.

Hermann determined that a mixture of streptococci and *B. coli* was more effective than *B. coli* alone.

The former investigators advocate the use of a single intraperitoneal injection of 30 c.c. of 1% gum tragacanth in normal saline solution containing about 200 million heat-killed *B. coli* per cubic centimeter. (Coli-bactragen).

Following Hermann's and Steinberg's work, the use of a vaccine containing both *B. coli* and streptococci was started 8 years ago at the Mayo Clinic and a marked reduction in mortality reported from its use by Rankin and Bargen. This group continues its pre-operative use in colon cases. Some unfavorable reactions following its use have been reported. (See 1934 Transactions, Intraperitoneal Vaccination, Jones' discussion).

Potter's and Coller's experience has been favorable with Coli-bactragen (Steinberg) in 79 cases.

Gundel and Sucssbrich have treated 240 cases of peritonitis with "peritoneal serum" and have studied the cases bacteriologically. They used a polyvalent serum containing colon bacillus, gas gangrene bacillus and enterococci. They state that of 51 patients given this serum for prophylaxis or treatment, 6 died but 5 of these had heart or lung complications.

Young and Marks have used amniotic fluid concentrate in a series of 48 cases of colon resection with a mortality of only 2% in the whole group. They regard the beneficial effects of vaccines to be non-specific. A preparation of amniotic fluid is now on the market named Amfetin.

INSTRUMENTS

Bacon has devised a self-retaining illuminated proctoscope that is a short instrument tapering from the base to an expanded portion at the end, this expanded portion being grasped by the sphincter holds the instrument in place. It can also be used with a light adaptor, thus making it more generally available. He has also devised a stricturoscope consisting of a set of five tubes varying in calibre from ½" to ¼". By means of these the stricture can be calibrated, dilated, or treated before medicaments are applied. It is illuminated and has an adjustable lens which may be swung into place as desired.

DIVERTICULITIS

Various theories continue to be considered in an effort to determine the exact mode of formation of colonic diverticula. *d'Abreu* believes spasm and hyperactivity of the circular muscle of the bowel to be factors of great importance and he suggests that excessive parasympathetic action is a cause of these particularly inasmuch as relief is obtained by belladonna and hyoscyamus.

Edwards reserves surgery in diverticulitis of the colon for severe recurrent cases in which complications appear to be imminent. A right side colostomy should precede resection and should be done between attacks.

Weible suggests allowing diverticulitis of the sigmoid to go to abscess formation, then drainage being made through the anterior rectal wall by a tube extending through the anus.

Weber stresses the importance of contrast enemas after the method of Fisher and the insufflation of air following expulsion. Diagnostic efficiency is dependent upon the examiner's familiarity with the gross pathologic features of lesions as well as methods of examination.

Stewart and Illick in an article on the roentgenographic differentiation between diverticulitis and cancer of the sigmoid bring out several points of interest in a well illustrated article. They used but a pint of barium at first, examined the rectum and sigmoid thoroughly, thus avoiding confusion by other loops. The colon is then filled, and the entire procedure repeated after the patient has partially emptied the colon and again after complete defecation, often 24 hours after passing, as diverticula may be seen at this time which were not previously visible.

Lynch records a case of diverticulitis of the colon with abscess formation caused by an enema tip injury.

CONSTIPATION

Beck in "The Management of Chronic Spastic Constipation" gives a general review of the subject. Chronic constipation progresses usually through three stages: atonic, catarrhal, and spastic. The latter is perhaps the commonest variety for which the physician is consulted. He lists the causes as constitutional, eating habits, diet, cathartics, neglect, diseases, e.g. of stomach, liver, intestines, anaemia, functional neuroses, and others. Treatment is given in detail. *Spencer* does not hesitate to start his paper with "Constipation is a symptom not a disease," trite though it may be. He considers the subject from the standpoint of the physiology and the pathological physiology concerned. Associated causes may be failure to respond regularly to the urge to defecation, dietary factors, cathartic abuse, sedentary habits, obstruction from bands, and adhesions usually causing right sided stasis; stasis from emotional states, irritating food residues, lead, tobacco, caffein, organic diseases of the lumbar cord and inflamed mucosa, however caused.

In his discussion of spastic constipation he does not support the classification atonic and hypertonic (spastic). "There is little or no evidence for atonic constipation." He describes the spastic type as a definite entity and cites *Buckstein's* grouping based on stasis proximal to some particular sphincter or in a definite segment of bowel. A very rational therapy is described.

CONGENITAL ANOMALIES

Kantor describes a logical procedure to assist in locating the blind end of the rectum in imperforate anus. After a colostomy has been functioning satisfactorily, a catheter on a catheter guide is passed through the colostomy stoma into the lower segment and after incision of the anal depression a finger is passed upward to palpate the end of the catheter.

Rhodes reports a case and discusses the method of caring for this condition.

A colostomy in an infant is less satisfactory than in older patients; even so in case of complete atresia it offers the infant a better chance for its life than blind exploration to locate the rectum if the blind end is much separated from the anus.

Kantor records his study of 2000 cases of anomalies of the colon. He classifies them as follows: Redundancy, Non-rotation, Hypodescent, Hyperdescent, Hypofixation

and Hyperfixation. Unless obstruction occurs these should generally be treated conservatively. Symptomatic treatment is all that is usually required.

Gardner and Hart state that a knowledge of normal intestinal rotation is important to an understanding of the possible abnormalities. They report 2 cases of volvulus of the entire mesentery giving symptoms of duodenal obstruction and review 103 reported cases.

SECTION VIII—*Editorial*

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastro-enterological Association is in no way responsible for editorial expressions.

THE UNKNOWN LIVER

REPORTS of new procedures designed to test liver function accumulate month by month in the literature, evidence of a desire to learn more of the functions of this organ which so well hides the secrets of its behavior. And yet we must still depend primarily upon the old criteria, jaundice and enlargement, for clinical evidence of pathological changes in this organ. We do not know the cause of death after hepatectomy when adequate glucose is supplied. And the liver is now the only organ of which this can be said; in all other cases we can either provide effective substitution or adequately explain the fatal effects of removal.

One reason for the slowness with which information concerning hepatic physiology accumulates is the diversity of functions possessed by the liver; it takes an important or essential part in the metabolism of fats, carbohydrates and proteins, stores vitamins and antianemic factors, is concerned in regulating the volume and concentration of the blood, influences the mineral metabolism, and synthesizes numerous substances for excretion into the bile or in the process of detoxification.

Until recently there has been no suggestion that the liver is specifically influenced by any hormones except epinephrine and insulins. The only other regulating mechanism that has been known is the nervous system, which controls the deposition of glycogen, liberation of glucose, and caliber of the hepatic vessels. Since the demonstration by Houssay that hypophysectomy reduces the glycosuria, hyperglycemia, and ketosis of experimental diabetes, further investigation has indicated that this effect is mediated largely, at least, through the liver. Adrenalectomy has a similar effect upon the diabetic animal, but replacement therapy by anterior pituitary extracts, which restores ketosis in the hypophysectomized-depancreatized preparation, has no effect when the adrenals and pancreas have been removed (1). This suggests that the absence of the hypophysis affects the diabetic state by causing cessation of adrenal activity, and that an adrenal hormone is primarily responsible. The adrenalel cortex is known to atrophy after hypophysectomy.

But whether the effect is direct, from an hypophyseal hormone, or indirect, by way of the adrenals, it is becoming apparent that a hormone is essential for the normal activity and function of the liver. This has been suggested by Best (2) and is emphasized again by Long (3) in a recent brief review of endocrine activity and metabolism. The hepatic tissue is presumably the sole site of formation of the ketone bodies; ketosis ceases after removal of the hypophysis and can be restored by injections of anterior lobe extracts. In the liver, also, glucose is constantly being manufactured from amino acids, lactic acid, and other non-carbohydrate sources; this process of gluconeogenesis likewise fails after hypophysectomy and to its failure we can attribute, at least in part, the decrease in glycosuria and hyperglycemia of the hypophysectomized diabetic animal.

These contributions, while of the utmost value to our conception of the problems of diabetes, offer at present no ray of hope for rational therapeutic application. Even though the functions of the liver can be suppressed by removal of an essential hormone (and it has long been known that hepatic injury can produce an amelioration of the symptoms of diabetes), there appears no justification for so suppressing hepatic activity, thereby treating one metabolic disturbance by the production of another.

Lathan A. Crandall, Jr.,
Northwestern University, Chicago.

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A "NEWS" SECTION FOR THE JOURNAL

MEN who work in similar or allied fields like to, (and *should*) know what is happening among their confreres.

Thus far, the JOURNAL has been concerned with so many problems of organization, distribution, technical questions, and the multitudinous variety of matters ever appearing when a magazine is launched, that many desirable, yet not absolutely essential, activities have had to be postponed.

Now that this publication has made for itself a place in the world's literature and the mechanics of printing and circulation well are in hand, opportunity presents itself for a "breathing spell" and the consideration of what may be pleasing, yet not strictly necessary.

A number of contributors—in this and other lands—has urged that a "News" section be provided. Such section will include items of national and international interest; happenings to physicians and scientists, in practice, at institutions for teaching and research, in medical organizations, and so on, as suitable activities occur. A "gossip column" is not intended or desired, but *real news* dealing with matters of consequence would seem worth the space given to it.

In proportion to the response from our subscribers, such "News" section will be valuable. We invite the submission of material. It must reach the Editor before the first day of any month. Brevity, accuracy and "news value" are desired.

We bespeak hearty cooperation.

Frank Smithies.

SECTION IX—*Book Reviews*

(This section is open to contributions from any medical reader, whether or not a member of the Editorial Council).

Experimental Enzyme Chemistry. Henry Tauber, Ph.D. Burgess Publishing Company, Minneapolis, Minn., 1936. 130 pages, illus. (11 x 8 in.) Fabric. Price: $3.50.

THE biochemistry of the digestive fluids and tissue juices is occupying the forefront of medical knowledge and experimental investigation. It is impossible, today, adequately to explain the so-called vital phenomena without a thorough comprehension of the chemical processes which are responsible for biologic manifestations.

Nowhere is this more true than in the field of gastro-enterology. Not only is the physiology of digestion, absorption and utilization of the various food elements dependent upon the chemistry of the digestive juices and of the cells lining the gastro-intestinal tract. The manifestations of disease also are intimately bound up with these factors which furnish a proper understanding of some of the normal as well as pathological symptoms associated with the function of the stomach and intestinal tract and its complementary glands.

It has long been known that enzymes elaborated and secreted by the cellular aggregates play a very important role in these processes. Dr. Tauber's book is a distinct contribution in this field because it summarizes the present day knowledge on the subject in a very succinct and clear manner. As a basis for diagnosis the information which can be culled from this book is of inestimable value. The bibliography is very extensive and fairly complete. As the author says in his preface, it is not possible to review all the work of recent years; but the bibliography certainly does more than that.

While this book contains considerable chemical data and many formulae, it describes many enzymes in a simple enough manner, so that even the non-technical medical man can add greatly to his knowledge of this complicated and little known subject.

In Chapter I with the Introduction, the book deals with definition of an enzyme and a discussion of the effect of temperature, hydrogen ion concentration, effect of excessive substrate, and the discussion of activators and inhibitors, and the views concerning the chemical nature of the mechanism of action. The author quotes Bechhold's analogy of the living cell as: "A city in which colloids are the houses and crystalloids are the people who transverse the streets, disappearing into, and emerging from the houses and those who are engaged in erecting or demolishing buildings. The colloids are the stable part of the organism, the crystalloids the mobile part, which, penetrating everywhere, may bring weal or woe."

It might be added that enzymes are the tools or instruments by which this is accomplished in producing changes without themselves being incorporated into these changes.

Chapter II deals with esterases derived from pancreas, stomach, liver, and certain plants, and tannase, sulphatase, and phosphatase.

Chapter III deals with proteolytic enzymes and peptidases. The structure of the enzymes is discussed, and differentiation between proteases derived from the stomach and the pancreas is made. Microphotographs of these individual enzyme crystals are clear and exceedingly well reproduced. In this chapter the subject of crystallization is given in detail. Plant proteases are also discussed in this chapter.

Chapter IV deals with amidases which act upon amino acids, and acid amids. In this chapter urease is discussed at considerable length.

Chapter V deals with carbohydrases, the carbohydrate splitting ferments which have probably been studied more extensively than any other type of enzyme. This chapter not only discusses the various saccharases, but also discusses the glucosidases and emulsin, and those enzymes which split starch and glycogen. The identification of molecular structure by means of enzymes receives attention in this book, and the reader is referred, for the considerable amount of information which could not possibly be included in this small book, to the extensive bibliography which follows each chapter.

Chapter VI deals with catalases.

Chapter VII deals with oxidizing enzymes which are subdivided into the anaerobic group and the aerobic group. A subject of considerable importance, particularly in the true oxidase group, is a discussion of the Vitamin C oxidase of ascorbic acid. The ferment which oxidases ascorbic acid is of tremendous importance in the light of the role which this Vitamin plays in the cure and prevention of disease and its relationship to the chemical processes associated with maintenance of normal physiology.

Chapter VIII deals with the oxidation system associated with coenzymes, and which belong in the group of dyes such as flavine, as well as other colored enzymes.

Chapter IX deals with the carbonic anhydrase which is associated with the liberation of carbon dioxide into the capillaries of the lung.

Chapters X and XI discuss the enzyme chemistry of alcoholic fermentation and bioluminescence.

This book therefore is of value, not only to students of nutrition, but also to physicians who seek satisfactory explanation for many of the symptoms which they observe in connection with gastro-intestinal and nutritional disturbances.

Benjamin Jablons, New York City.

The Patient and the Weather. Volume 1, Part 2. William F. Peterson. Edwards & Co., Publishers, Ann Arbor, Mich., 1936.

THIS big volume of nearly 800 pages rather overwhelms one—it represents such an enormous amount of work and it covers such an enormous field. One marvels at Dr. Peterson's industry and his devotion to his subject and his knowledge of the literature.

He is convinced that changes in weather can account for almost any change that ever takes place in the health or in the bodily functions of a man. The book is filled with complex graphs showing the relations between temperature curves, barograms, storms, etc., and changes in bodily chemistry or pulse rate or blood pressure or what not.

The average physician is prepared to receive the information that arthritic joints become more painful as storms approach but he will probably be a bit surprised when told that his patient died on a certain day after operation because an anticyclone or something came along. He will want to have more proof of this and if he does not find it, he is likely to lose faith in the author. As we have said in reviewing previous volumes issued, it would be most regrettable if after all this tremenous labor by Doctor Peterson and his colaborators, the medical world should "walk by" as the reviewer has had to do, and say, "We marvel at the man's industry; we hope he has proved his thesis; we wish we could spend weeks and months in examining the graphs so that we could tell whether or not the facts justify the conclusions, but after reading here and there for a few days and running into many things that look to us more like chance and coincidences than proofs, we hesitate to spend more time on the book—we'll let someone else make an analysis and a more readable abstract of it."

This would be most regretable. Unfortunately, it is extremely difficult for the human mind to judge of complicated graphs such as are published in this book. It is too hard to remember after studying twenty curves how many times the lines ran parallel and how many times they ran higgledy-piggledy, or one line went up while the other went down. The visual method is too precarious and too widely open to self-deception. Our impression is that the statistician's method of correlation is the only one that will ever bring order out of chaos in these books and will show in a minute what degree of relationship there actually was between two sets of data. When there is a perfect relationship, either positive or inverse, between, let us say, barometric pressure and blood pressure, the index will be either plus 1 or minus 1, and when there is no agreement the index will approximate 0.

If Doctor Peterson wants his enormous labors to influence medical practice and if he wishes his books to be read and his theses accepted, it would seem as if he ought to get a statistician to calculate the indices of correlation for the data now published in the form of curves. Then the men who are competent to pass on Peterson's work and to appraise it can pick out in a few moments the experiments that showed a correlation between weather and bodily functions. Even then, however, much room will be left for judgment as to whether or not an experiment was run long enough to prove anything. If an experiment is so short as to cover only one episode, as many of Peterson's are, it may be suggestive, but that is all. What is the use of showing that an epileptic attack coincided with an anti-cyclonic storm? For that matter, even the method of correlation has its dangers. Thus one might find that the curve representing increased use of electric refrigerators in the United States parallels beautifully the curve representing the national debt of Japan, and yet one couldn't say that one was cause and the other effect.

All of which does not keep us from recommending this book to all of those who like to think. It is crammed with information and suggestion, and for a medical book, it is unusually well written. The main criticism is that it confuses through its very richness. It would have been more convincing if it had had fewer illustrating protocols and more careful analyses and explanations of the ones presented. Peterson would have helped his cause much by leaving out protocols of the many inconclusive experiments, some so inconclusive as to throw doubt on the good judgment of a man who would show them at all.

Walter A. Alvarez, Rochester, Minn.

SECTION XII—"*The Clinic*"

Intestinal Polyposis: Adenomatosis Coli and Polyposis Cystica Intestini*

By

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NEW YORK, NEW YORK

THE term "intestinal polyposis" has sometimes been used indiscriminately to describe two separate and distinct clinical and pathological entities, namely, *adenomatosis coli and polyposis cystica intestini*. The purpose of this communication is to differentiate these two conditions.

1. *Etiology.* There are two main theories as to the etiology of adenomatosis coli, both of which have much to support them. Ribbert (1) suggests their origin in embryonal rests, a theory intimately connected with oncogenesis in general. Versé (2), Ewing, Lockhart-Mummery, Dukes (3) and others propose an inflammatory basis for the development of these multiple tumors without excluding some *anlage* peculiar to the individual or family. The consensus of opinion appears to be that the condition has a definite hereditary tendency of the Mendelian type. Every specimen in our series falls in this group, two or more members of the

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Submitted September 11, 1936.

family having had the condition, three generations having been involved in one instance. Polyposis cystica intestini, however, involves no hereditary factor. Evidence has recently been presented indicating that the disease is acquired and is the late result of bacillary dysentery (4). The similarity lies only in the familial incidence which is wholly explainable in polyposis cystica on the basis of contact infection during the early stage of acute bacillary dysentery. In follow-up studies of more than 200 cases of acute bacillary dysentery not one instance of adenomatosis coli has been encountered. This suggests that if a chronic inflammatory process precedes the neoplastic one, it is probably not due to bacillary dysentery.

2. *Pathology.* Adenomatosis coli is characterized by the development of multiple solid adenomata of the mucosa of the colon. We have never seen these tumors extend beyond the ileocecal valve although involvement of the small bowel has been described by Lubarsch

TABLE I

Differential features of intestinal polyposis

Polyposis Cystica Intestini	*Adenomatosis Coli*
1. Inflammatory.	1. Neoplastic.
2. Acquired.	2. Hereditary factor.
3. The late result of bacillary dysentery.	3. Etiology unknown.
4. Mucosal ulceration, mural fibrosis and stenosis involving entire segment of bowel.	4. No mucosal ulceration or mural fibrosis. Stenosis, if present, is local and due to size of tumor or desmoplasia associated with malignancy.
5. Does not become malignant.	5. Multicentric malignancy frequent.
6. Process often extends beyond ileocecal valve into ileum or may involve any part of the small or large bowel in segmental fashion.	6. Generally limited to colon.
7. Loss of haustration.	7. No loss of haustration.
8. Ideal therapy is the prevention of bacillary dysentery.	8. Ideal therapy is complete resection.

(5), Niemack (6), Ribbert (7), Petrow (8) and Hauser (9). Other types of tumors, however, may occur concomitantly in the small bowel, such as leiomyoma or lipoma. Gatersleben (10) reports a case of multiple polyposis of the small intestine with malignant degeneration in a woman of 22 and states that this is the fourth case of polyposis in this location to be reported in the literature. Adenomatosis coli represents a neoplastic process, the tumors beginning as small, punctate, flattened elevations of the mucous membrane scarcely visible to the naked eye. Slowly increasing in size these areas become larger and more rounded. The surface appears smooth and reddened, but close inspection of the larger tumors generally reveals a division into closely-knit cauliflower-like lobules. The typical fully developed adenoma is mushroomed at the tip of some redundant mucosa, eventually becoming more and more pedunculated because of traction on a loosely attached mucous membrane and underlying submucosa. Sometimes these pedicles, which consist of mucosa and underlying vascularized connective tissue, become quite long, a tumor located in the sigmoid not infrequently appearing at the anus. The process probably is the result of an attempt by the bowel to expel the tumor as it would a foreign body. The pedunculated tumors are generally benign. When malignancy supervenes the tumor which originally had a short pedicle becomes sessile, spreads laterally, undergoes central necrosis and eventually takes on the appearance of adenoma malignum or adenoma destruens. It seems quite certain that they remain local for a relatively long time, are only slowly invasive and, when resected at a reasonably early period, do not recur. Most of the cures of carcinoma of the colon probably fall in this group. These tumors, whether adenomatous or malignant, are well vascularized and are prone to repeated hemorrhage. The blood vessels are located in the connective tissue core which is generally continuous with the submucosa of the bowel. The pedicles, which consist of mucosa and submucosa, may undergo torsion with subsequent partial or complete necrosis of the adenoma. Inasmuch as adenomatosis coli is a condition in which the adenomata are scattered all over the colon, malignancy may occur simultaneously in several tumors—a true example of multicentric malignancy (11). This can be readily shown in the case of two such tumors by means of serial sections of the intervening intestine. There is no undermining of the mucosa by spread of cancer cells along the submucosal lymphatic plexus and reappearance at another point of the intestine. Each nidus is separate and distinct. We have never seen adenoma malignum or adenoma destruens in the small bowel associated with adenomatosis coli, a condition which should be encountered if adenomatous polyps occurred with any appreciable frequency in the small intestine. The rarity of primary carcinoma in the latter is well known. Aside from the tendency to multicentric malignancy in adenomatosis coli the condition seems to be associated with some underlying pathological *anlage* or tendency to the development of other intestinal pathology. Indeed, this is the rule in nearly all neoplastic diseases of the colon. Thus, villous tumors, submucosal lipomata or diverticula are often associated lesions. Another differential point is the absence of ulceration between the polyps, the intervening mucosa generally being quite normal. Whether adenomatous polyps are the precursors of all carcinomata of the bowel, as suggested by Schmieden and Westhues, Fitzgibbon, Rankin and others is perhaps still somewhat debatable. However, this view has been misinterpreted by many to mean that all adenomatous polyps become malignant. This, of course, is not so. The same mistaken point of view existed not so many years ago with regard to ulcers of the stomach becoming carcinomatous. The incidence of multiple, silent, benign, adenomatous polyps in our necropsy series is 3.03% in 462 successive necropsies (4.1% excluding 119 babies). The figure increases in direct proportion to the care with which the intestine is examined in the autopsy room. The earliest histopathologic changes suggesting malignancy appear to be loss of ducts, imbalance of stroma and glands, atypical glandular morphology, multiplication of cell layers, nuclear hyperchromatism and penetration of the muscularis mucosae. Even after this occurs it should be remembered that the submucosal lymphatic plexus often acts as an effective barrier to the further spread of the disease for many months, perhaps as long as a year. The prognosis in this type of tumor, generally grade one, is

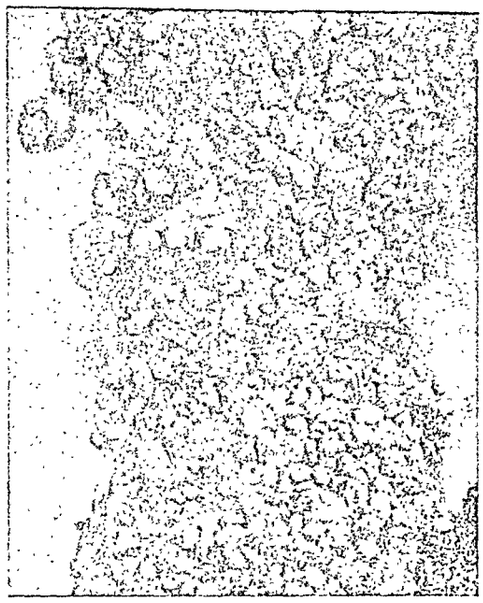


Fig. 1. No. 578. Adenomatosis coli in a male, age 45, in whom the chief symptoms were diarrhea and hemorrhage. Note both the sessile and pedunculated tumors in all stages of development with scarcely any normal mucosa visible.

therefore correspondingly good. Adenomatosis coli has never been observed in the newborn.

Polyposis cystica intestini has only the remotest resemblance in the gross to adenomatosis coli. The polyps on close scrutiny through the sigmoidoscope are seen to be pinched off bits of swollen mucous membrane with intervening areas of ulceration. The condition is inflammatory, not neoplastic and represents one phase in the development of the disease known as chronic ulcerative colitis. Contiguous intramural infection is always present and may be associated with intramural abscess formation, fibrosis or both. Often the solitary acuminate lymph nodules are totally destroyed and the colon becomes essentially a narrowed, thickened, infected, vascularized tube of connective tissue. Extensive linear, serpiginous and geographic areas of ulceration alternate with small or large areas of intact mucosa which, because of blockage of ducts by scar tissue and retained gland secretion, take on a polypoid appearance. They can hardly be regarded, however, as true polypi and in this sense the term is a misnomer. The colon may be involved in a segmental fashion and the process often extends into the appendix and beyond the ileocecal valve into the small intestine, particularly the distal portion of the ileum (chronic distal ileitis). Loss of haustration is always seen in the roentgenographic examination and diffuse stenosis of the bowel lumen is frequent. Bleeding in this condition occurs chiefly from the ulcerated areas, the infection eventually causing necrosis of the superficial vessels. Epidemiological, clinical, pathological, bacteriological and serological evidence point to polyposis cystica intestini as being the late result of bacillary dysentery. The original organism dies out and secondary non-specific infection occurs through the ulcers originally produced by B. dysenteriae. We have never seen malignancy directly attributable to or even remotely associated with this condition, although it has occasionally been described. Every case of polyposis in which we have seen this occur has been one of adenomatosis coli ante-



Fig. 2. No. 6443. Adenomatosis coli in a female, age 21. Arrow points to an associated villous tumor. Maternal uncle and maternal grandmother died of the same disease.



Fig. 3. No. 2604. Multicentric malignancy in descending colon and sigmoid in a male, age 38. Five years after resection there was no evidence of recurrence or metastasis. Other adenomata were present, but not removed. Upper tumor is a benign adenoma; middle and lower tumors are malignant.



Fig. 4. No. 7160. Chronic ulcerative colitis associated with polyposis cystica intestini. Entire mucosa is ulcerated except for the small scattered islands visible in the photograph. Original infection due to B. dysenteriae Flexner.



Fig. 5. No. 8179. Chronic ulcerative colitis, the late result of infection with B. dysenteriae Flexner. The mucosa is broken up into shreds and pseudopolyps (arrow). Note mural thickening at right edge of photograph.

dating and existing independent of an original infection with B. dysenteriae. Multicentric malignancy has never been noted in polyposis cystica intestini.

3. *Diagnosis.* The clinical diagnosis of adenomatosis coli is generally made by direct visualization of the tumors through the sigmoidoscope. One of the tumors may be snared off for microscopic study which shows the characteristic adenomatous structure. Roentgenographic examination reveals multiple smooth circular defects which projects into the column of barium. The diagnosis of polyposis cystica rests on the characteristic polypoid islands of mucosa with intervening areas of ulceration readily seen through the sigmoidoscope. During acute exacerbations a mucopurulent exudate may be seen and free bleeding is common. The bowel is stenosed due to extensive intramural fibrosis and roentgenographic study reveals a typical loss of haustration, mural thickening and defects in the mucosal pattern corresponding to the ulcerated areas lying between the polyps. Biopsy of these polyps shows only chronic inflammation, but *no evidence of neoplasia.* Even at this late stage one may occasionally recover B. dysenteriae if the organism is sought for persistently. Agglutination titer against B. dysenteriae usually positive if a sufficient number of strains are used in the tests.

4. *Symptomatology.* In adenomatosis coli, diarrhea, bloody intestinal discharges, cramps, anemia and loss of weight are common symptoms. In polyposis cystica intestini similar symptoms occur, but a careful history and epidemiological study often will reveal that the process is merely a perpetuation of an original acute bacillary dysentery. The intestinal discharges are not only bloody, but often purulent, indicating the inflammatory nature of the disease. Intramural abscess formation is common and is accompanied by a septic type of temperature which promptly subsides following evacuation of the abscesses. The natural course of the disease is one of periods of remission and exacerbation which appear to correspond to relatively high and low degrees of immunity to the primary and secondary infecting organisms.

5. *Therapy.* The treatment of adenomatosis coli is surgical—either a short circuiting operation to divert the fecal stream or complete colectomy. The latter operative procedure is attended with a high rate of mortality and should be undertaken only by experienced surgeons. Repeated blood transfusions before and after operation are helpful. Fulguration has been used successfully on adenomata in portions of the bowel which could not be resected. The ideal treatment of polyposis cystica intestini (chronic ulcerative colitis) is the prevention of bacillary dysentery. Once fully established, polyposis cystica intestini is extremely resistant to therapy. Every patient with acute bacillary dysentery who does not recover within three weeks should receive active immunization with D-C vaccine (Dysentery-Colitis vaccine containing polyvalent autogenous and stock strains of the original infecting dysentery organism, enterococcus, hemolytic and non-hemolytic B. coli). This procedure should be supplemented by D-C antivirus, intestinal oxygenation and repeated transfusions in which suitable individuals who have recovered from bacillary dysentery are used as donors. Immunization should be carried out intensively *before* the chronic lesions have been well established. Surgery has a very limited place in polyposis cystica intestini. Resections are attended with a relatively high rate of mortality and recurrences are frequent. The latter are due to cutting through infected bowel or overlooking "skip areas" of ulcerative colitis. Short circuiting operations do not clear up the infection and the use of a stoma for irrigation purposes is of very doubtful value.

SUMMARY

Adenomatosis coli and polyposis cystica intestini are two entirely different conditions. Epidemiological, clinical, pathological, serological and bacteriological studies indicate that polyposis cystica intestini is the chronic stage of acute bacillary dysentery. Adenomatosis coli, on the other hand, is a neoplastic disease prone to multicentric malignancy and unrelated to bacillary dysentery.

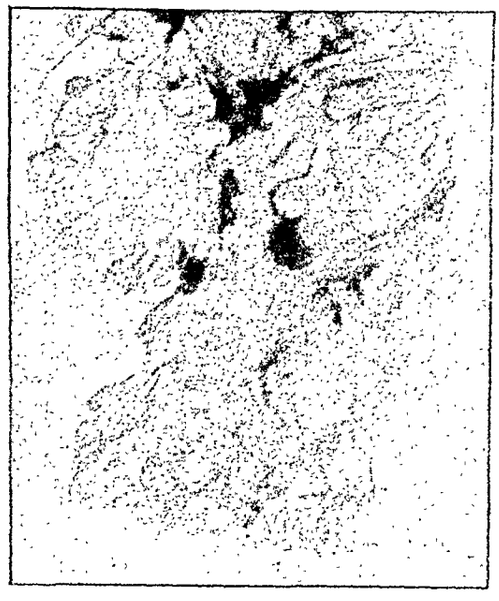


Fig. 6. No. 6180. Ulcerative, granulomatous and polypoid lesions of the sigmoid with obstruction. The pathology is similar to that seen in specimens 4 and 5.

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Diffuse Polyposis of the Colon*

A Case Report

By

L. K. FERGUSON, M.D.†

PHILADELPHIA, PENNSYLVANIA

VIRCHOW (4), in 1863, first described the form of diffuse polyposis of the colon, and later Cripps (1), in 1882, pointed out the familial tendency in this disease. Since that time many authors have reported isolated cases. Rankin (3) recently reported 11 cases which he treated by total colectomy, with 2 deaths. Janssen (2), in 1932, reported 2 cases of this disease in brothers, with the history that there was probably the same disease in the father. In an investigation of the family he also found 2 other cases.

The patient to be reported illustrates the characteristic symptoms of this disease. She was a young woman 37 years of age whose mother had died at the age of 45 with what was believed to be carcinoma of the rectum. She was markedly thin and emaciated, weighing about 90 pounds; the hemoglobin was 56%. She gave a history that for 9 years she had had attacks of diarrhea, lasting from 3 weeks to 2 months; between the attacks there were often periods of rather marked constipation. During the year before admission, the attacks were almost constant. The movements were liquid and as many as 8 to 10 a day and contained much mucus and often blood. On proctoscopic examination in November, 1935, the bowel wall was found to be literally covered with palpable and visible polyps. A barium enema showed a diffuse polyposis involving the entire large gut. (Fig. 1).

On admission to the hospital she was prepared for operation by several blood transfusions, and on December 14th, the abdomen was opened through a grid-iron incision on the right side. The ileum was sectioned, the distal end inverted, and a mushroom catheter was sewed into the proximal end and brought out through a muscle-splitting incision in the right rectus. At the time of operation a mass was palpable in the sigmoid; this was believed to be a carcinomatous degeneration of the polyps.

The patient did fairly well. Her fluid intake was augmented to about 3000 c.c. a day by the use of intravenous infusions and blood transfusions. The wounds healed by primary intention and the patient was up and about the ward for a time, but she became a psychological problem, refusing to eat solid food. At her own request, she was permitted to go home but her nourishment and care were not of the best and she steadily became weaker. She was readmitted to the hospital. Fluids were supplied in abundance intravenously and, in addition, four transfusions were



Fig. 1. Barium enema, showing diffuse polyposis throughout the entire large gut.

*Read before the Philadelphia Academy of Surgery, March 2, 1936.

†Associate in Surgery, University of Pennsylvania.

Submitted September 6, 1935.

given, but she never could be made to eat solid foods and finally died 45 days after operation.

This case is of interest in pointing out several difficulties which may arise in the care of such patients. In the first place, the preparation of the patient for operation must be a very thorough one. The patients are usually anemic and markedly dehydrated; fluids and blood must be supplied before operation may be performed.

Secondly, the postoperative care of patients with ileostomy cannot be treated lightly. The loss of fluids following operation is often considerable and it is important that an accurate estimate of fluid loss be kept in order to gauge the fluid intake.

Thirdly, as soon as possible, these patients should be permitted to eat solid food, in order to hasten the development of a colon-like hypertrophy of the terminal ileum, which in a measure reduces the fluid loss.

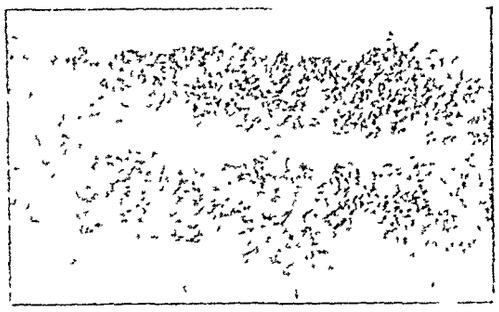


Fig. 2. Diffuse polypoidosis of large intestine with foci of adenocarcinomatous degeneration in the sigmoid. The upper section is the ascending colon, and the lower section is the sigmoid. Malignant degeneration was found in four areas (see arrows), from which sections were made.

Fourthly, the operation of choice in these cases is a resection of the colon or colon and rectum because of the almost certain danger of carcinomatous degeneration of the polyps. In this patient a carcinomatous degeneration had taken place in three of the masses. (Figs. 2 and 3).

Fifthly, Rankin's experience in handling these cases should be noted. Following a preliminary ileostomy, he permits the patient to regain strength and normal bowel function for a period of 3 to 4 months and then performs a colectomy in stages down to the sigmoid. He points out that in resection of the transverse colon, his best results have been obtained by dividing the posterior leaf of the transverse mesocolon so as to leave the greater omentum. In his later cases, he has attempted to leave the rectum and lower sigmoid, to remove the polyps in this area by effulguration. If he is successful in the latter procedure, he then forms an anastomosis between the ileum and the remaining sigmoid so as to again reform the continuity of the intestinal tract and to permit bowel movements per rectum.

SUMMARY

This patient presents the typical history, diarrhea in the young anemic patient, which is seen in diffuse polyposis. The disease is probably familial in this case, and had progressed to a carcinomatous degeneration of three of the polypoid masses. The problems arising in the treatment of such patients have been discussed.

DISCUSSION

DR. CALVIN M. SMYTH, Jr. It is very important to place cases of this type on record since no one individual sees a sufficient number to enable him to speak with much authority and it is only by referring to collective experience that anything can be learned regarding the proper method of procedure. Some years ago in a similar case we performed a terminal ileostomy and the patient improved rapidly. Without previous experience to guide us we resected his colon at the end of three weeks and the patient died. At the present time we have a young woman of 28 years who was admitted originally to the Medical Service with a grave progressive anemia, diarrhea, bleeding from the bowel and loss of weight. A diagnosis of diffuse polyposis was made by X-ray and sigmoidoscopy. After repeated transfusions we performed terminal ileostomy and her improvement has been truly remarkable. The terminal ileum is gradually taking over function of the large intestine and she is eating solid food and rapidly gaining strength. Naturally she is anxious to have the rest of her surgery done but with our previous experience and with the experience of others in mind, she is being sent home to wait for two or three months. Many surgeons fail to realize that ileostomy is a formidable procedure. For one thing the disturbance in water balance following it is sufficient to cause death and it is not only a question of replacing fluid but of keeping a close check on the electrolyte balance and gauging the administration of water, salt and sugar accordingly. One of the most important points brought out in Doctor Ferguson's paper is the necessity of a long period of waiting between the performance of ileostomy and colectomy. The latter should never be undertaken until one is perfectly sure that the maximum improvement has been obtained.



Fig. 3. Section of sigmoid polyp, presenting normal mucosa and adenocarcinoma, separated only by the thin villus of stroma.

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ABSTRACTS

CLINICAL MEDICINE

MYERSON, A., AND RETVO, M.

Benzedrine Surfate and Its Value in Spasm of the Gastro-intestinal Tract. J. A. M. A., Vol. 107, pp. 24-26, July 4, 1936.

The muscular activity of the gastro-intestinal tract, normal and abnormal, has interested physiologists, roentgenologists and clinicians because of its close relationship to the emotional state of the patient. Spasm of the gastro-intestinal tract arises from many causes. It may result from (1) functional disturbances, such as worry; (2) the neuroses and psychoses; (3) intrinsic disease of the gastro-intestinal tract, as a cancer, an ulcer or appendicitis; (4) extra-alimentary conditions such as renal colic, plumbism or tabes dorsalis.

Many drugs have been tried to abolish these spastic manifestations, among them atropine and benzyl benzoate, but results have been poor. In order that a drug be valuable it must fulfill the following requirements: (1) the effect should not be prolonged; (2) it should not cause unpleasant or dangerous reactions; (3) it should be rapidly and uniformly effective when given orally, as some patients may object to injection methods; (4) the routine roentgen studies should not be interfered with; (5) it should be generally available and inexpensive.

Benzedrine in the form of the sulfate has been tried and has been found to lessen or abolish spasm of the gastro-intestinal tract within a few minutes after its oral administration. It is said to act on the sympathetic system and therefore is a sympathicamimetic drug. The spasm is relieved when due to unpleasant emotion, organic disease of the tract, or reflex spasm from organic disease elsewhere in the body. This facilitates roentgenographic differentiation between functional and organic spasm, and gives better visualization of organic lesions. The drug has also been used clinically in the relief of spastic colitis and pylorospasm.

Francis D. Murphy, Milwaukee.

SANDWEISS, DAVID J.

Treatment of Gastro-duodenal Ulcer with Histidine Monohydrochloride. J. A. M. A., Vol. 106, pp. 1452-1459, April 25, 1936.

The treatment of peptic ulcer by the Sippy method, by modifications of it, or by surgical intervention is unsatisfactory in many cases. There are many cases which respond at first, but then relapse. Whether this response to treatment is merely coincident with a natural remission in the course of the ulcer, or whether it is actually a response to treatment is not known.

Many new methods of treatment have recently been advocated. Among these is the injection of histidine intramuscularly. The La Rostidin brand of histamine (histidine monohydrochloride) is the most widely advocated product for this.

The rationale of this treatment, according to Weiss and Aron following their work on dogs, is that ulcers develop because of a deficiency of the amino acid histamine. Their experimental work does not prove this conclusively; in fact, similar work by other workers points in a different direction.

Sandweiss, working on sixty-seven patients with peptic ulcer, of which fifty-three were treated with the diet-alkali regimen, and forty with histidine, had the following results:

1. Of the patients treated with diet-alkali, 51 per cent became symptom free and 20.7 per cent were moderately improved. Of the patients treated with histidine, 55 per cent became symptom free and 20 per cent were moderately improved.

2. Of seventeen patients treated with histidine after failure to respond to the diet-alkali management, 52.9 per cent became symptom free and 17.6 per cent were moderately improved.

3. Of nine patients treated with the diet-alkali after histidine failed, 42.8 per cent became symptom free and 28.6 per cent were moderately improved.

4. By changing from one treatment to another, 73.5 per cent became symptom free and 13.4 per cent were moderately improved. Of the nine patients not responding to medical treatment, four required surgical intervention and five had medical complications, such as myocarditis, hyperthyroidism or arteriosclerosis.

5. Eighty-five per cent of the patients treated with histidine had remissions after six months, and 31 per cent of those on the diet-alkali regimen had remissions after six months.

6. Twenty-four consecutive daily injections of histidine are not essential to produce a remission or prolong a symptom-free period. If eight injections at the most do not produce a disappearance of all symptoms, further injections will not be of great value.

7. About one-third of seventeen patients showed a slight increase in the acid curve; one-third showed a slight decrease; and one-third showed no change.

8. Twenty-four patients who were checked either by X-ray or operation after histidine treatment did not show any disappearnace of the ulcer deformity.

9. Sixteen of the patients treated with histidine developed mild reactions.

The conclusion was reached that, because of results paralleling those obtained in the diet-alkali treatment, histidine was of value only as an accessory in the treatment of those cases which do not respond well to the diet-alkali method.

Francis D. Murphy, Milwaukee.

MOUNT, G., MOUNT, F. R., *and* HUNTER, W. C.

Calcification in the Spleen. J. A. M. A., Vol. 107, pp. 203-205, July 17, 1936.

Calcification in the spleen usually occurs in small zones, in the capsule, in small infarcts, and in tuberculous or gummatous masses. It also occurs in thrombosis of the splenic vein, echinococcus cyst, and in diseases associated with extensive general calcification.

The following is the history of a woman, aged 44, who over a period of two years complained of an uncomfortable feeling of pressure in the left hypochondrium, which during the last six months was aggravated by eating, stooping forward and lifting of the left arm. Three months previous to the onset of these symptoms she was in an automobile accident in which she injured her left side just below the ribs.

Physical examination revealed a mass in the left hypochondrium which was apparently the spleen. This was confirmed by the fluoroscope. Splenectomy was done and the patient made a satisfactory recovery.

Examination of the spleen revealed a large calcified mass in the hilus, which mass extended into the substance of the spleen leaving only a small area of normal spleen at the upper pale. Microscopic examination revealed large calcified areas surrounded by areas of hyaline degeneration. The etiology of this condition was thought to be trauma, at the time of the automobile accident, with rupture of the splenic pulp without tearing of the capsule, followed by organization of the hemotoma which formed with the later deposition of calcium salts.

Francis D. Murphy, Milwaukee.

EXPERIMENTAL PHYSIOLOGY

FITZ-HUGH, THOMAS, JR.

Experiments with "Depepsinized" Human Gastric Juice in the Treatment of Pernicious Anemia. Am. Jour. Med. Sciences, p. 168, August, 1936.

After discussion of work done by Roger Morris and his associates, Minot and Castle, Wilkinson and Vlados, Fonts and Zerfas and Greenspon, the authors report their studies in three cases of pernicious anemia, in relapse, with red cell counts between 1.4 and 2.3 million and hemoglobin from 40 to 58% (Sahli). The diet was iron-free. Gastric juice concentrates for parenteral administration. "Depepsinization" was carried out by the method of Fenger and Andrews as recommended by Greenspon. Normal gastric juice was obtained from ward and clinic patients with normal blood counts, normal gastric acidity and without evidence of tuberculosis, syphilis or other active infection. The first patient, a woman, was given an injection of 11 c.c. of a concentrate representing 200 c.c. of fasting "depepsinized" gastric juice from her own stomach during the preceding week. Reticulocyte fluctuation, for 10 days before and 6 days thereafter, varied between 0.2% and 1.3%. This was considered a completely negative result. This experiment was undertaken with the thought that if Morris' so-called addisin produced merely non-specific irritation effects rather than true "hormonal stimulation there would be no apriori reason why pernicious anemia juice might not be as effective as normal juice.

A second experiment on this same patient consisted of introducing into her stomach 500 c.c. of pooled normal "peptically inactivated" fasting gastric juice through the stomach tube. Then food was withheld for 5 hours and before it was taken, gastric lavage was repeated. 3 days later another 500 c.c. of normal gastric juice was given by tube. The reticulocyte count showed a slight increase to 4% on the 3rd day after the first gastric juice feeding; i.e., on the day of the second feeding. One day later reticulocytes were 5% and then fell in 6 days to 1% and the red cell count and hemoglobin were slightly lower than before any experiments were begun. This patient later showed the usual hematologic recovery on a parenteral potent liver extract. The observation was not considered as proof of anything.

Experiment 3 was on a man and lyophilized P.A. gastric juice was used as a concentrate intramuscularly. This was followed by a local and systemic reaction. Reticulocytes rose from 2.1% before the experiment, to 4.7% on the 12th day after the injection but the red cells and hemoglobin declined.

Experiment 4 consisted of giving this same patient 11 c.c. concentrate of the acetone soluble fraction of lyophilized normal fasting gastric juice. This was followed by a reticulocyte rise from 1.4% to 3.5%; the red cells and hemoglobin remaining unchanged.

Experiment 5 consisted of giving intramuscularly 12 c.c. concentrate of 700 c.c. of normal "depepsinized" human gastric juice. No favorable effect was observed.

Experiment 6 consisted of parenteral injection of a concentrate of the patient's (pernicious anemia in relapse) own gastric juice. In 4 and 8 days respectively, reticulocytosis of 4.5% and 5.3% were observed but otherwise there was no change in the blood picture.

Experiment 7, the same patient, received a concentrate of normal depepsinized gastric juice without effect. In Summary, all the procedures with depepsinized gastric juice failed to excite a significant reticulocyte response in the cases of pernicious anemia the authors studied.

Allen Jones, Buffalo.

ROENTGENOLOGY

MERRITT, E. A., AND RATHBONE, R. R.

The Diagnosis and Roentgen Treatment of Carcinoma of the Head of the Pancreas. Radiology, Vol. 26, No. 4, April, 1936.

Merritt and Rathbone state that of all the neoplasms which are observed to occur in the pancreas, carcinoma is by far the most frequent. Sites of predilection are the head, the body, and the tail of the organ respectively. . Hoffman, in 1934, set the mortality from cancer of the pancreas at not less than 3 per cent of the total mortality from all forms of malignant diseases in the United States.

The cause and nature of carcinoma of the pancreas is presented briefly. The symptomatology and pathology of carcinoma of the pancreas are discussed and the surgical treatment.

The authors present the history of a white woman, aged 47 years, with a history of epigastric disturbances during the previous two years, followed by a recent appearance of painless jaundice, with clay-colored stools and vomiting. At operation the gall bladder was enlarged and tense, but no stones were found. The head of the pancreas was very hard and nodular; the tail of the pancreas was soft. The liver was enlarged; no metastases were noted.

Roentgen therapy was advised. In the first series, extending from August 30 to September 18, 1933, the patient received a total dosage of 4,500 r (2,250 r to the anterior and 2,250 r to the posterior pancreas). The tumor dose was 1,800 r. The following factors were used: 220 kvp., 20 ma., 50 cm., distance; Thoraeus tin filter equivalent to 2.0 mm. copper, 250 r (measured in air) to alternate 15 x 15 cm. anterior area and 20 x 20 cm. posterior area. The authors report that the patient's general condition improved during treatment and the vomiting stopped.

In July, 1935, the patient ran a septic temperature and became very toxic and died August 3, 1935. The autopsy revealed a terminal pneumonia, multiple metastases of both lungs, abscess of liver, hepatitis, chronic cholecystitis and cholelithiasis. There was no malignancy of the pancreas; it showed a chronic interstitial pancreatitis.

In the summary, the authors state that clinically the patient presented evidence of carcinoma of the pancreas and this was verified by surgical exploration. A cholecysto-jejunostomy was done to relieve the biliary obstruction. The patient was given intensive postoperative roentgen therapy with complete disappearance of the tumor and apparent clinical recovery for a period of one year when she developed signs and symptoms of liver metastases. No evidence of malignancy was found at autopsy. The authors present this case to stimulate further trial of roentgen therapy in carcinoma of the pancreas.

D. S. Beilin, Chicago.

ABDOMINAL SURGERY

BLAHD, M. E.

Surgical Indications for Peptic Ulcer and Its Surgical Management. S. G. O., Vol. 62, No. 2, pp. 203-212, Feb. 1, 1936.

In addition to obstruction, perforation and severe uncontrollable hemorrhage, the author proposes a fourth positive indication for surgery in the treatment of peptic ulcer. He concurs with Boas of Berlin in the belief that the character of the ulcer and not the number of medical cures should be the factor to determine the need for surgical treatment. He feels that the penetrating type of ulcer is rarely if ever cured under a medical regimen and that when it is demonstrated roentgenographically as a fleck in a crater it constitutes the fourth positive indication for surgery.

Subtotal gastrectomy is proposed as the operation of choice, securing upward of 90 per cent of permanent cures.

Statistics of the primary mortality following gastric resection show that it is higher than that of gastro-enterostomy, but when the secondary mortality following the latter procedure is taken into consideration there is very little difference. The secondary mortality following gastric resection is practically nil.

Pre-operatively a medical regimen designed to build up the patient is followed for a period of time. Gastric lavage is recommended. Some form of regional anesthesia is preferred. A detailed description of a posterior Polya type of gastrojejunal anastomosis as

modified by Finsterer is given in detail. The stomach is sectioned at right angles to the body axis so as to favor rapid emptying and prevent regurgitation from the afferent jejunal loop.

Postoperatively nothing is given by mouth during the first five days; venoclysis of 3,000 cubic centimeters of 2.5 per cent glucose in normal saline is given daily. If gastric distention occurs, drainage is instituted by a Levine tube. The diet is enlarged until at the end of three weeks the patient leaves the hospital with no restrictions whatever upon his food.

Eleven figures and a bibliography accompany the article.

Nelson M. Percy, Chicago.

MENTZER, STANLEY H.

Obstructive Cholecystitis — With Particular Reference to Acute Obstructive Cholecystitis and Its Sequelae. S. G. O., 60:879-887, May, 1936.

The term "acute obstructive cholecystitis" is suggested for the suddenly obstructed and acutely inflamed gall bladder which is still filled with bile. "Hydrops" and "empyema" are used to designate the obstructed gall bladders filled with mucus or pus. While these two conditions result from prolonged obstruction, they are subject to acute and subacute exacerbations. Acute cholecystitis may occur at times without obstruction. The indicated treatment depends to a large extent upon the differentiation between the obstructive and non-obstructive lesions and to a lesser extent upon the differentiation of the various types of acute obstruction. The history of biliary distress, the presence of a tender mass, the height of the fever curve, and the degree and character of the leucocytosis should aid in making a satisfactory differentiation. Often, however, this seems quite difficult and if the fever, tenderness, rigidity, and leucocytosis persist under observation of 6 to 48 hours, the case should be considered as an advanced, acutely inflamed and obstructed gall bladder requiring immediate surgical attention. Jaundice is not an important symptom. Waiting for a subsidence of the acute infection is a dangerous form of conservatism accompanied by an increased incidence of perforation and an increased mortality. The operation of choice from the standpoint of immediate mortality as well as subsequent morbidity is cholecystectomy rather than cholecystostomy.

J. Duffy Hancock, Louisville.

DIXON, CLAUDE F., AND OLSON, PAUL F.

Twenty Year Cures of Carcinoma of the Colon. S. G. O., 62:874-879, May, 1936.

Hopeful encouragement is offered by considering those patients surviving operation for carcinoma of the colon rather than those dying of the disease. Reporting twelve such persons still living or having lived for 20 years after the removal of the growth is especially significant when the normal expectancy of most of the patients in this group is considered. The fact that two had additional resection of the small intestine and one of the bladder at the time of the colonic resection gives additional evidence that these cases are far from hopeless. An interesting incidental finding was the confirmation of the feasibility of grading carcinoma. Every one in this series had been graded 1 or 2. To put it another way, no patient with a colonic carcinoma graded 3 or 4 survived a 20 year period. Further, only three of the twelve cases showed metastasis to the local lymph nodes. In a study of the entire group of 453 cases, it was shown that there was an increasing incidence of local metastasis with the higher grades. In other words, that metatasis was twice as frequent in primary lesions of grade 4 than it was in those of grade 1. These findings seem rather conclusive so far as grading is concerned.

The ability to give specific instances of 20 year cures as reported in this series of microscopically proved cases should offer much consolation to patients having this type of malignancy.

J. Duffy Hancock, Louisville.

RED CROSS HEALTH WORK

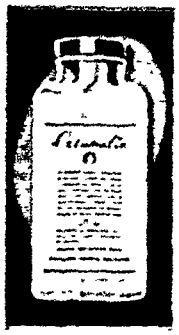


WORKING in cooperation with local public health authorities the Red Cross carries on each year hundreds of immunization programs in communities threatened with serious epidemics of typhoid and other communicable diseases. An unusually large amount of this preventive work was done this year in the wide areas affected by floods. Many of these communities were without suitable drinking water in the mains for a number of days and although every precaution was taken to see that all drinking water was boiled it was deemed wise to carry on extensive immunization as a further safeguard.

In addition to its medical and health work on disaster scenes the Red Cross maintains a year-round Public Health Nursing service, which brings the visiting nurse to hundreds of small towns and rural communities where medical and hospital facilities are at a minimum. Not only through her nursing care of, but also by her instruction to mothers and girls in Home Hygiene and Care of the Sick does the public health nurse assist the country doctor to safeguard health in these sparsely populated districts.

All Red Cross services are supported by the annual membership dues of millions of Americans who join each year during the Roll Call, held from Armistice Day to Thanksgiving. Everyone is invited to have a part in the work of their Red Cross by enrolling in their local Chapter.

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CLEVELAND CHEMICAL ASSOCIATES

3616 Euclid Avenue Cleveland, Ohio

ABELL, IRVIN

The Surgical Treatment of Peptic Ulcer. Ky. Med. Journ. 34:286-290. July 1936.

The treatment of peptic ulcer is primarily a medical problem, surgical procedures being required for the complications, sequallae, and intractable chronicity. Surgery, regardless of the type of operation, should be directed towards a restoration of physiological function, free drainage of the stomach, partial neutralization of the stomach acids by intestinal alkalies, and the destruction or removal of the ulcers or ulcers. The three generally accepted indications for operation are perforation, hemorrhage, and obstruction. In acute perforation, prompt closure is the prime indication since the seriousness of the condition is controlled by the stoppage of the leak. Further procedures at such a time will depend not only upon the pathology presented, but more upon the condition of the patient. Chronic perforations, more or less successfully closed by nature, will present individual problems for treatment. Some hemorrhage will occur in approximately 25 per cent of all cases of gastric and duodenal ulcers. The immediate treatment should be rest in bed, physiological rest of the stomach, fluid and nutrition in the form of glucose and whole blood transfusions, and coagulants, chiefly fibrogen by mouth. If operation is done, destruction of the ulcer is imperative regardless of the type of procedure adopted. A single massive hemorrhage, particularly from a duodenal ulcer, is not usually an indication for operation unless other complications, as obstruction, are present.

In the surgical treatment of duodenal ulcers, simple excision alone is inadequate. Gastroenterostomy or pyloroplasty, either combined with cautery destruction of the ulcer are the usual measures employed. Resection is reserved for those cases with multiple ulcers, with calloused ulcers on the posterior wall, or with perforation into the head of the pancreas with fixation.

Gastric ulcers present the same surgical indications as do duodenal ulcers with the additional serious possibility of malignant change. Small resectable ulcers, 1 centimeter or less in size, may be treated by the conservative excision or cauterization combined with gastroenterostomy—never by gastroenterostomy alone. Larger ulcers, those with marked inflamatory deposit, those with healed perforations into adjacent structures and those with perigastric adhesions, require more radical treatment—sleeve resection, Billroth I, or the Polya modification of Billroth II where very wide resection is indicated.

Permanency of cure is dependent not only on the proper selection and proper technique of operation, but also upon the elimination of extra-gastric factors such as possible foci of infection and the adherence to correct dietary and medical supervision after the operation.

J. Duffy Hancock, Louisville.

DRENNEN, EARLE

Diet and Surgery in the Cure of Gastric and Duodenal Ulcers. South. Med. Journ. 29:699-701. July 1936.

Peptic ulcer is primarily a medical and not a surgical disease. The ideal time for medical cure is when the ulcer and the patient are both young. Two habits contributing to the formation of peptic ulcers are smoking of tobacco and drinking of alcohol; the predisposing cause, which is quite important, is the tendency towards ulcer which certain individuals inherit; and the exciting causes are hyperacidity, toxins, and neurogenic factors. Failure of medical treatment may be evidenced by disabling pain and indigestion, severe hemorrhage, perforation, obstruction, and malignant change. The aims of operative treatment of benign lesions are the proper drainage of the stomach and the lowering of acidity. The usual operations are gastroenterostomy, partial resection, and pyloroplasty.



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While gastroenterostomy is quite satisfactory in many cases, it has a serious disadvantage in the possibility of jejunal ulcer. Partial resection is increasing in popularity, but it is yet too early to evaluate its true worth. Pyloroplasty which leaves the digestive tract more normal anatomically and which is less likely to be followed by serious sequellae appears to be the author's preference at the present time. Best results from any kind of operative treatment are expected in those cases where there is no family history of ulcer, the patient is middle-aged, the acidity is low, the emptying time slow, and the duration of symptoms and treatment rather long.

J. Duffy Hancock, Louisville.

CONNELL, F. G.

Duodenal Ulcer, Surgical Treatment. S. G. O., Vol. 62, No. 2, pp. 216-217, Feb. 1, 1936.

From a review of the development of the surgical treatment of non-resectable duodenal ulcer the author is led to believe that two operations, namely: (1) exclusion with resection of pylorus and antrum and also circumferential resection of part of the fundus, and (2), exclusion with circumferential resection of part of the fundus but without resection of the pylorus and antrum are equally satisfactory. Why then, he asks, remove the pylorus and antrum in resectable duodenal ulcer? Since it does not seem important to resect the pylorus and antrum the author suggests "partial fundusectomy." It has the advantage of leaving intact the antropyloroduodenoneuromuscular mechanism and diminishes the acid secreting area. The ulcer might or might not be resected. If there is pyloric obstruction an additional plastic operation there must be made.

The author observes that peptic ulcer is now recognized as a physiological problem in which there is a lack of balance between an agressive (acid) and a defensive (alkaline) factor.

The author is of the opinion that any operative procedure should be followed by postoperative medical management.

Eight figures accompany the article.

Nelson M. Percy, Chicago.

ELIASON, E. L., AND JOHNSON, J.

Life Expectancy in Biliary-Intestinal Anastomosis. S. G. O., Vol. 62, No. 1, pp. 50-56, Jan., 1936.

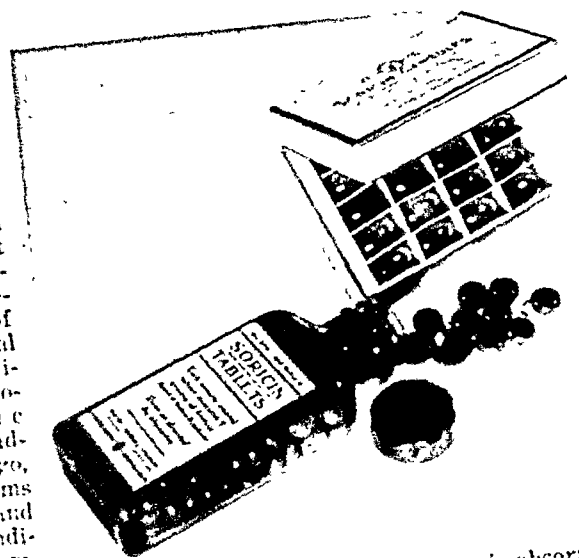
In a review of the experimental work done on biliary-intestinal anastomosis the author points out that ascending liver infection is an almost constant sequel. Some workers report it in 100 per cent of the cases. Others have found it less frequently.

It is generally agreed that the position of the anastomosis should be in the stomach or duodenum and not lower in the intestinal tract because the danger of infection is greater in those situations.

The operation is indicated in cases of common duct obstruction from carcinoma, chronic pancreatitis, stricture or traumatic injury of the ducts or stone in the common duct that can not be removed. Cholecysto-gastrostomy has been recommended as an alternative procedure for cholecystectomy, as a method of drainage in cases of cholangitis and in the treatment of gastric ulcer.

In cases of malignant obstruction of the common duct life expectancy may be increased by only a few months. Those few months are more bearable, however, by the relief of jaundice and its attendant discomforts. In cases of non-malignant obstruction of the common duct life expectancy may be normal. A number of patients with such conditions have died, within a few years, of ascending liver infection. Ascending liver infection is a frequent enough complication following this operation to prevent its indiscriminant

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ure. The usefulness of biliary-intestinal anastomosis in non-malignant conditions can not be evaluated at this time.

Three tables and a large bibliography accompany the article.

Nelson M. Percy, Chicago.

DIXON, C. F., AND OLSON, P. F.

Twenty Year Cures of Carcinoma of the Colon. S. G. O., Vol. 62, No. 5, pp. 674-678, May, 1936.

The authors believing that it might add to the peace of mind of those of us who may be afflicted with malignant disease in the future if more emphasis were laid on the curability of the disease and more specific instances were reported as definite proof of that contention, reports in some detail the operative and pathological records of a dozen patients who lived more than twenty years after eradication of carcinoma of the large bowel. A most exacting observer, it is admitted, might not regard these as actual cures. For those who might properly raise some question concerning the original diagnoses new microscopic sections made from the specimens after resting twenty-five years in formalin solutions have been made. Those sections confirm the original diagnoses.

Of these twelve patients, two were operated on when in their third decade; six, in their fourth decade; three in their fifth decade; and one at the age of 64. Eight of the patients were men and four were women.

In all of these cases the grade of malignancy was low. A further study of a group of 453 specimens showed the presence of metastases in the regional lymph nodes and the length of post-operative survival to be shorter in those of higher grades of malignancy. Metastases to regional lymph nodes were found to occur almost twice as frequently from primary lesions that were grade four malignancy than from those which revealed a malignancy of grade one.

Six figures accompany the article.

Nelson M. Percy, Chicago.

WILSON, W. D., LEHMAN, E. P., AND GOODWIN, W. H.

Prognosis in Gall Bladder Surgery. J. A. M. A., Vol. 106, pp. 2209-2213, June 27, 1936.

Recognition of the deficiencies of gall bladder surgery from the point of view of complete relief of symptoms has troubled both surgeons and internists. It is agreed that although the place of surgery in the treatment of a large group of cases with gall bladder disease is established, in another group the benefits of surgery are not so obvious.

Six hundred and ten cases operated on over the period of years between 1921 and 1931 by twenty surgeons at the University of Virginia Hospital were studied. The mortality rate was 3.6 per cent.

Questionnaires were sent to the patients (except the 22 who died in the hospital) and replies were received in 417 cases. The interval between the treatment and the questionnaire varied from four months to thirteen years. The patients were questioned concerning (1) general health, (2) recurrence of symptoms, (3) food tolerance, (4) hernia, (5) capacity for work, (6) their estimate of the effects of treatment.

The method used by these authors demonstrates no statistical significance in comparisons between the symptomatic results and such factors as age, sex, race, duration of symptoms, severity of symptoms, presence or absence of jaundice, presence or absence of a history of colic, the degree of functional disturbance indicated by the cholecystogram, the pathologic stage of the disease and the type of operation.

The conclusions reached are as follows:

A. Cholelithiasis presents satisfactory clinical results in 7.5 per cent of

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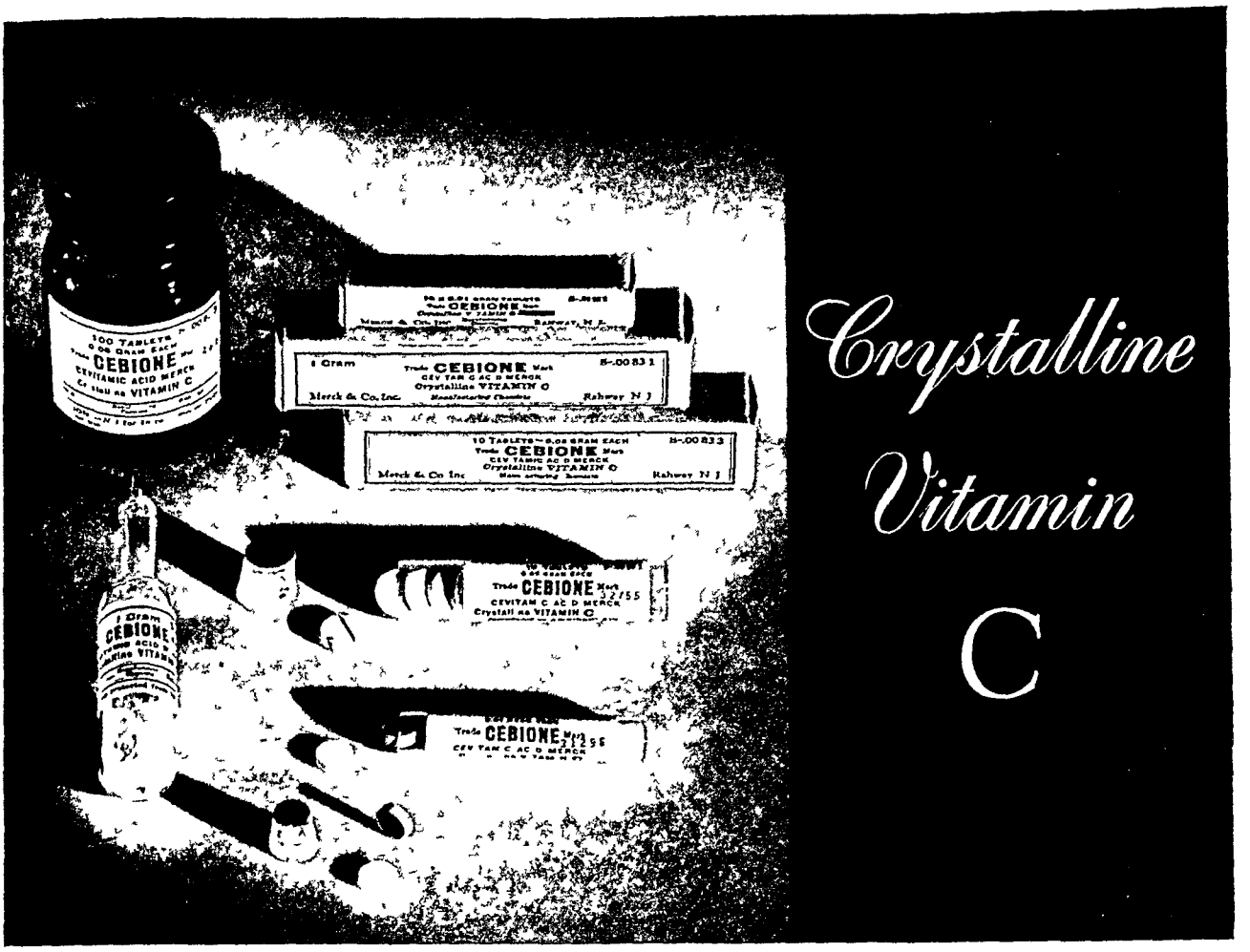
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cases; cases without stone in 61 per cent.

B. Cases that show a marked degree of pathologic alteration of the gall bladder wall present satisfactory clinical results in 82.2 per cent of cases; with moderate degree of alteration, 76.6 per cent; with a mild degree, 57 per cent.

C. The cholecystogram is a significant index of the degree of pathologic change in the gall bladder.

D. The desirability of early operation in acute cholecystitis is not proved when measured by mortality rates.

Francis D. Murphy, Milwaukee.

HERBST, R. H., AND MILLER, E. M.

Vesico-Intestinal Fistulae Caused by Foreign Bodies in the Bowel. J. A. M. A., Vol. 106, pp. 2125-2128, June 20, 1936.

Vesico-intestinal fistulae are of rather frequent occurrence when due to diverticulitis or malignancy, but very rare if the fistulae are due to foreign bodies. In a review of the literature it was difficult to determine whether the foreign body traveled by way of the gastro-intestinal tract, whether it became lodged in a diverticulum, resulting in a diverticulitis, adhesion to the bladder and finally perforation by ulceration, or whether the foreign body was introduced into the bladder through the urethra, and thence into the intestine.

The author reports a case of a man who for six months complained of frequency, urgency, dysuria, nocturia, hematuria, chills, fever, and had loss of 25 pounds of weight in this time. Examination revealed a large fixed mass in the median line above the pubis. Cystoscopic examination revealed a markedly injected bladder, a foreign body in the floor which when removed consisted of vegetable matter, and a brown spot on the posterior wall of the bladder with a depression in the center. This spot suggested a fistula but a catheter would not pass, and sodium iodide introduced into the bladder could not be vistualized in the intestine. Preoperatively, a diagnosis of carcinoma was made. At operation a large mass was found and removed. The center of this mass contained a large, curved, sharp-pointed chicken bone.

This is a typical case of vesico-intestinal fistulae, and shows the value of cystoscopic examination in all cases of prolonged cystitis.

Francis D. Murphy, Milwaukee.

KIPP, H. A.

Observations on the Variations in Bile Pressure in the Human Biliary Tract. J. A. M. A., Vol. 106, pp. 2225-2227, June 27, 1936.

Observations of the bile pressure in a 78 year old man were made. The patient had been jaundiced for more than two years. At operation a benign stricture of the common bile duct at the ampulla of Vater was found. A cholecystogastrostomy was performed and a T tube was placed in the common duct. The convalescence of the patient was stormy, but after about three months he was discharged from the hospital. The T tube was left intact because of the age, the general condition of the patient, and the fear of an ascending infection.

The author thought that if the pressure of the bile in the T tube was not high, and if it was no higher when erect than when laying down, the tube could be removed safely. With this in mind, he arranged a manometer with a 4 mm. inside diameter and a scale in inches, and connected it to the T tube.

The average of the pressure on inspiration was 6.28 inches (159.5 mm. of bile) and on expiration was 5.7 inches (142.5 mm. of bile). It was also noted that when the patient took a deep breath the pressure was raised on both



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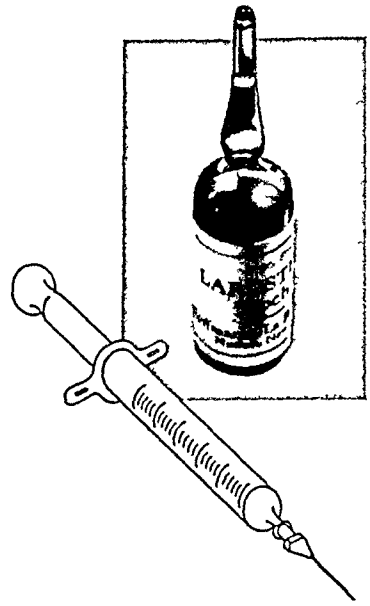


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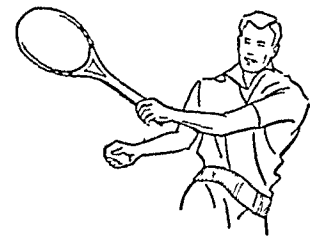
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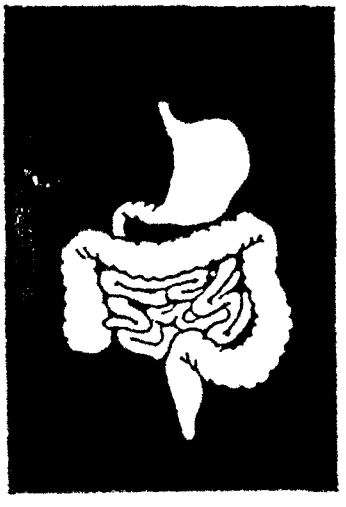
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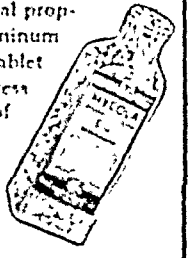
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inspiration and expiration. Coughing also increased the pressure to a considerable extent. Laughing also produced some rise in the pressure. The feeding of a fatty meal was accompanied by a slight rise in pressure, probably, and to increased peristalsis. After these tests were made, the patient was allowed to stand up and the pressure *rose to 13½ inches on inspiration* and 12½ inches on expiration. This elevation postponed the removal of the T tube for another year.

At this time similar observations were noted. Therefore the T tube was still left in place for another three months, at the end of which time it was removed. This was followed by a healing of the wound in eighteen days and apparently no impairment of function of the cholecystrogastrostomy.

Francis D. Murphy, Milwaukee.

McGOWAN, J. M., BUTCH, W. L., AND WALTERS, W.

Pressure in the Common Bile Duct of Man. J. A. M. A., Vol. 106, pp. 2227-2230, June 27, 1936.

Recently the importance of the function of the sphincteric mechanism at the lower end of the common bile duct and the clinical application of the knowledge concerning it in the management of biliary tract disease have been receiving a great deal of attention.

With this in view, the authors have made a series of observations of the changes in pressure in the common bile duct on individuals with a T tube in the common bile duct for the purpose of prolonged biliary drainage. The pressure was measured by a spinal fluid manometer connected to the T tube.

Studies of the pressure were made on fifteen occasions; the subjects were eight different patients, all of whom were at rest during the studies. Respiratory excursions caused the pressure to rise from 5 to 10 mm. of water. Morphine sulfate, it was found, in doses of one-sixth grain, subcutaneously, produced an increase in intraductal pressure on fourteen occasions. The pressure began to rise in from two and a half to four minutes after the administration of morphine. In one case it was associated with constant pain. This pain became increasingly severe for the first ten minutes and was followed by a gradual decrease in severity, probably due to the action of the morphine on the higher centers.

The cause of the pain offers a large field for speculation. It was noticed, however, that fluid could be made to flow from the common bile duct into the duodenum after the administration of morphine only by increasing the pressure. Roentgenograms showed evidence of rapid emptying of the duct before morphine and distention after its administration.

It was thought that muscle spasm might be the cause of the pain. In accordance with this various drugs were administered to combat it. It was found that atropine, histamine, phenobarbital, sodium, alcohol or acetylsalicylic acid



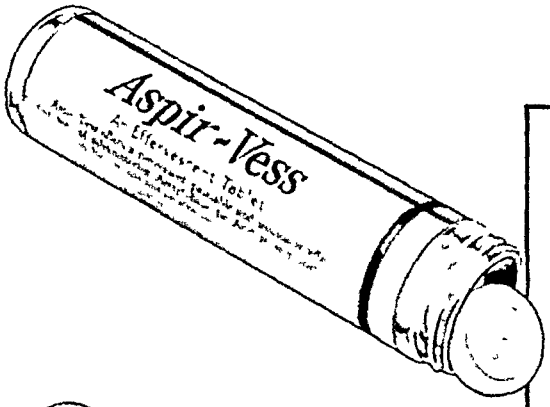
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produced no effect. Amyl nitrite produced a fall in pressure to zero, followed by a rise to the level before the administration of the morphine. Glyceryl trinitrate produced an effect about one-third as good as the amyl nitrite.

Francis D. Murphy, Milwaukee.

MALS, V.

Jejunostomy as a Palliative Procedure in Inoperable Obstructive Carcinoma of the Stomach. S. G. O., Vol. 62, No. 6, pp. 960-963, June, 1936.

Jejunostomy as a palliative procedure in inoperable obstructive carcinoma of the stomach should be done only after careful exploration of the entire abdominal cavity. The author prefers the upper left paramedian incision and nitrous oxide and oxygen or ethylene anesthesia.

A loop of jejunum, usually the upper 12 inches, are sought for and delivered through the incision; care being taken to determine that its mesentery is not twisted. The Eiselsberg-Witzel type of jejunostomy is made and its upper end secured to the anterior abdominal wall at the point where it lies without tension.

No pre-operative care is required. Post-operatively water may be given in small quantities within a few hours. A diet best for jejunal digestion as outlined by Ivy should be prescribed. Aspirated gastric juices and vitamin preparations may be mixed with the pabulum. If the tube is removed accidentally it may be re-inserted readily.

Five figures and a short bibliography accompany the article.

Nelson M. Percy, Chicago.

HINMAN, F., MURPHY, W. K., WAYMAN, T. B., MCCORKLE, H. J., AND BENTEEN, F. H.

An Experimental Study of Uretero-Intestinal Implantation. S. G. O., Vol. 62, No. 6, pp. 909-917, June, 1936.

The authors, in a study designed to determine the cause of peritonitis following uretero-intestinal anastomosis, performed that operation simultaneously bilateral in a large series of dogs. Ten different methods were employed. Contamination of the operative field was made in several instances and did not seem to affect the course of the animal post-operatively. Leakage, post-operatively, at the site of direct, as opposed

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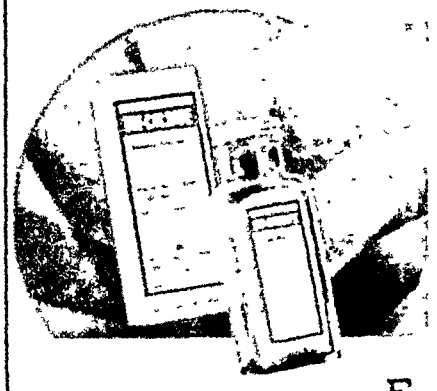
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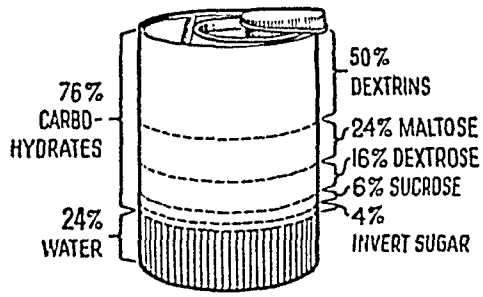
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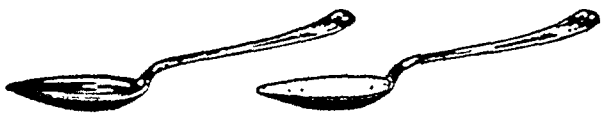
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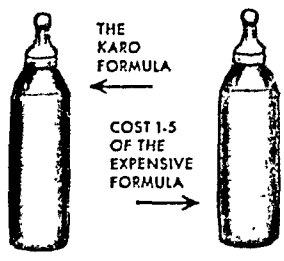


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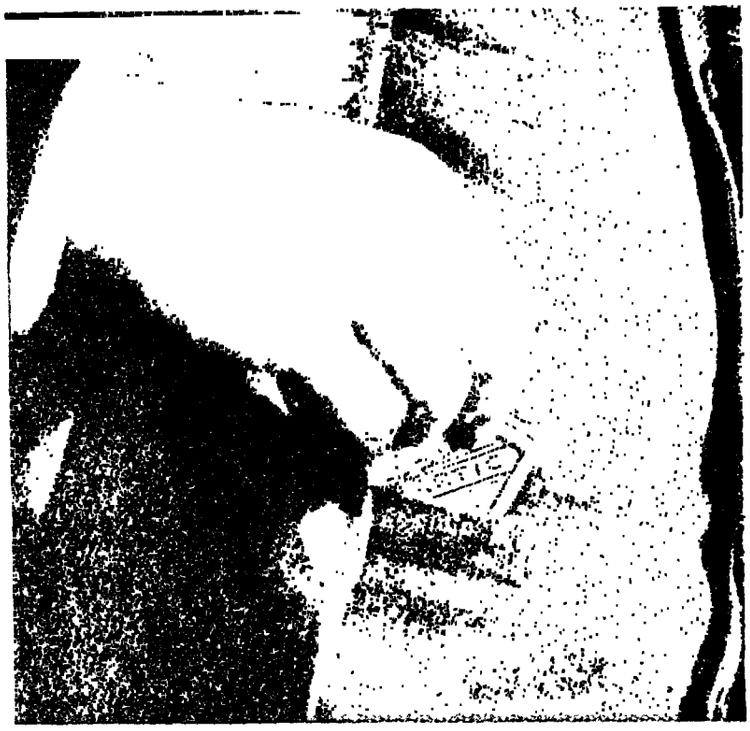
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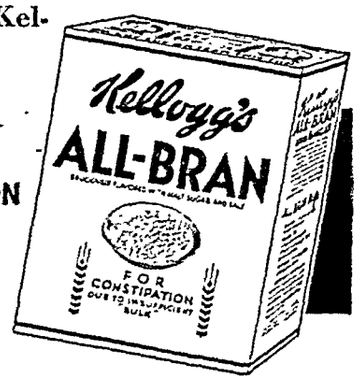
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to oblique. Implantation was followed by peritonitis and death of the animal in every instance. In 23 of 53 animals rather severe infection of the abdominal wound developed and was followed by death from ivisceration, peritonitis, etc. Localized abscess around the anastomosis occurred in two instances and was the origin of peritonitis in two others.

The author concludes that leakage or contamination at the time of operation is relatively unimportant, but that leakage from sloughs or tears after operation is the chief cause of peritonitis. The oblique method of implantation is preferable to the direct method.

Two tables and eight figures acompany the article.

Nelson M. Percy, Chicago.

McNEALY, R. W., AND LICHTENSTEIN, MANUAL E.

Gastrojejunostomy Pre-operative Decompression. S. G. O., 63:96-98, July, 1936.

Poor function of a gastrojejunostomy stoma may result from the fact that the stoma is usually made in a dilated stomach where elongated muscle fibres shorten in length after relief of the obstruction. Because of this and because, further, of the difficulty presented in suturing the thickened and edematous walls of such a dilated stomach, pre-operative decompression by continuous aspiration is suggested. The proper time for operation after the institution of such drainage is indicated by the development of a "positive pyloric balance," that is, when the amount of aspirated material is less than the amount taken by mouth, showing that the stomach is normally evacuating some of its contents. During this time of preparation, the nutrition, hydration and chemical balance of the patient should be cared for. In addition to these usual measures, some benefit may be derived from the administration of 60 to 80 minims of dilute hydrochloric acid given three times a day in 30 cubic centimeters of the juice expressed from raw beef diluted with an equal amount of water.

J. Duffy Hancock, Louisville.

DONALD, J. M.

"The Treatment of Acutely Perforated Duodenal Ulcer by Excision with Pyloroplasty." South. Med. Jour., 20:827-833, August, 1936.

There is unanimity of opinion in favor of immediate operation in cases of acute perforation of peptic ulcers. Duodenal ulcers are approximately ten times as frequent as gastric ulcers in this country. True pyloric ulcers are extremely rare—when the pylorous is involved, it is usually by an extension of a duodenal or gastric ulcer. Since ten to twenty percent of duodenal ulcers perforate, and since most patients with perforation gave an ulcer history, the prevention of perforation is best accomplished by adequate treatment of the ulcer early in its history. After the catastrophe occurs, the most common surgical procedures used are (1) simple closure, (2) simple closure plus gastroenterostomy, (3) excision wth pyloroplasty, and (4) subtotal gastrectomy. Simple closure has been recommended since it is the least possible amount of operative interference that can give relief and many feel that no more should be done in these desperately ill patients. On the other hand, it can be said that the severity of the symptoms usually brings the patient to the surgeon before there is much shock, a high percentage of the patients are not permanently relieved of their ulcer symptoms, there is danger of some degree of post- operative pyloric stenosis, and closure of the friable edematous tissue is not always as simple as it sounds. Gastroenterostomy is indicated where there is marked pyloric stenosis present at time of perforation, but has the disadvantage of late complicating gastrojejunal ulcers. Partial gastrectomy is generally regarded as an unnecessarily radical procedure for the type of ulcer found in this country.

While the operative measure used should be individualized to the conditions present, local excision with some form of pyloroplasty deserves more consideration. Different types of pyloroplasty are quite satisfactory but the one devised by Judd for non-perforated duodenal ulcers and described by him as "gastroduodenostomy" seems the most satisfactory. It is applicable in most cases, since the ulcer is usually found from 1 to 1.5 c.m. from the pyloric ring, stenosis and fixation of the pylorous are usually not present, and it requires only a few more minutes than simple closure. It offers the advantages of a gastroenterostomy without the possibility of marginal ulcer, it avoids constriction of the pylorus, and it results in the removal of friable tissue which may cause subsequent leakage where only simple closure is done. The procedure consists in the excision of a rectangular area including the cap of the duodenum, the ulcer, and the anterior half of the pyloric muscle, and the restoration of the normal continuity of the gastrointestinal tract by transverse closure. The mortaliy of the series described and also that of other series treated by this or some other form of excision and pyloroplasty are appreciably less than the usual 20 to 25%.

J. Duffy Hancock, Louisville.

JACOB K. BERMAN, WITH THE TECHNICAL ASSISTANCE OF NEAL E. BAXTER

Duodenogastric Intussesception — An Experimental Study of Peptic Ulcer. Arch. of Surgery, Vol. 33, 1-18, July 1936.

In an article introducing a new experimental surgical procedure into the study of peptic ulcer the author discusses the effects of this operation upon the gastric acidity and the quantity of gastric mucin produced in the stomach of three dogs and the influence of the operation in protecting the stomach and duodenum from experimental ulceration.

The technical procedure is to produce an intussusception of the first portion of the duodenum into the pyloric end of the stomach. The pyloric sphincter is first divided and the duodenum is invaginated into the stomach to a point proximal to the ampulla of Vater. The stomach and duodenum are sutured together exteriorly in this new relationship and the patency of the canal is tested.

The purpose of this experiment is based upon the assumption that there are two functions of the secretion from the Brunner's glands of the duodenum. The first of these functions is to produce a local protective mucin and the second to produce a hormone which causes an increase of gastric acidity. Increased acidity is in turn, according to the work of Florey and Harding, thought to cause a further production of the protective mucin. Thus Brunner's glands have an important role in the control of gastric acidity as well as a profound influence upon the protective mechanism of the gastro-duodenal mucosa.

Six determinations of free and total acid and of gastric mucin were made on each of three control dogs and on three dogs after the above operation was performed. The acidities were definitely higher in those animals having had the duodenal invagination. The gastric mucus was increased grossly and was very tenacious so that ample material for study could not be withdrawn through a Rehfuss tube. This increased acidity occurred in spite of the fact that there was free regurgitation of both bile and alkaline duodenal secretions into the stomach.

In another group of experimental animals the authors produced experimental ulcers in control dogs by the administration of Cinchophen, and in some having had a Finney pyloroplasty and in others having had duodenal invaginations. Acute hemorrhagic ulcerations were produced in all control animals. Ulceration and perforation occurred in at least one dog in which a Finney operation

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had been done. Only one dog upon which duodenal invagination had been performed developed an ulcer. This dog showed no increase in acidity after the operation as did all others which received Cinchophen. The authors believes that a failure to respond with an increase in gastric acidity indicates that this animal failed also to produce a sufficient amount of protective mucin, hence an ulcer developed.

They conclude that it is more likely a failure of this protective mechanism than an increase in acidity which may be responsible for peptic ulcer in man. The breakdown of this mechanism is thought to be due to an inactivity of the Brunner's glands of the duodenum. It is theorized that in the premonotory stage of peptic ulcer the administration of hydrochloric acid might stimulate these glands and increase the mucin protective activity of the gastric mucosa. It is also suggested that the operation of duodenal intussusception may become of value in the surgical treatment of peptic ulcer in man.

B. D. Rosenak, Indianapolis, Ind.

MACGUIRE, D. P.

Palliative Colostomy. S. G. O., Vol. 63, No. 1, pp. 66-68, July, 1936.

The author, prompted by a recent report of a seemingly inordinately high mortality rate following palliative colostomy, warns the general surgeon and occasional operator to give his undivided attention to each individual case. He points out the importance of daily blood chemistry determinations, blood cultures, blood counts, and urinalysis.

A method of palliative colostomy in which a tongue of skin, subcutaneous tissue and aponeurosis supports the exteriorized portion of bowel and prevents herniation beneath it is described.

Ten figures accompany the article.

Nelson M. Percy, Chicago.

MCNEALY, R. W., AND LICHTENSTEIN, M. E.

Gastrojejunostomy. Pre-Operative Decompression. S. G. O., Vol. 63, No. 1, pp. 96-98, July, 1936.

The authors, believing that too little emphasis has been placed on the preoperative treatment of patients with pyloric obstruction, point out some important considerations and report a means of restoring the stomach to a near normal state. Suture of a dilated, hypertrophied and edematous stomach wall is difficult and treacherous. Likewise, a gastro-enterostomy stoma in the proper place in a dilated stomach is apt to be too small and in an improper position when that stomach contracts to normal size. To decompress the stomach pre-operatively and allow it to return to a near normal state the authors have constructed a suction apparatus which is a combination of the methods suggested by Wangensteen, Bartlett, Babcock, Pratt and Peluse. By comparing the volumes of materials aspirated from the stomach from time to time with those of materials taken by mouth it will be apparent that the pyloris is either patent or closed. When the volume of material aspirated is less than that taken by mouth the "pyloric balance" is said to be "positive." Hourly recordings of aspirations and materials taken by mouth may be charted to show the status of the pyloris at any time. Operation should not be undertaken until the "pyloric balance" is 'positive."

Three figures accompany the article.

Nelson M. Percy, Chicago.

CARTER, R. FRANKLIN.

When to Remove the Drainage Tube in Common Bile Duct Drainage. S. G. O., 63:163-170, August, 1936.

The time for the removal of the drainage tube in common bile duct drainage has not been based upon very

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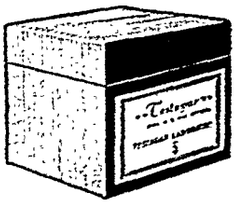
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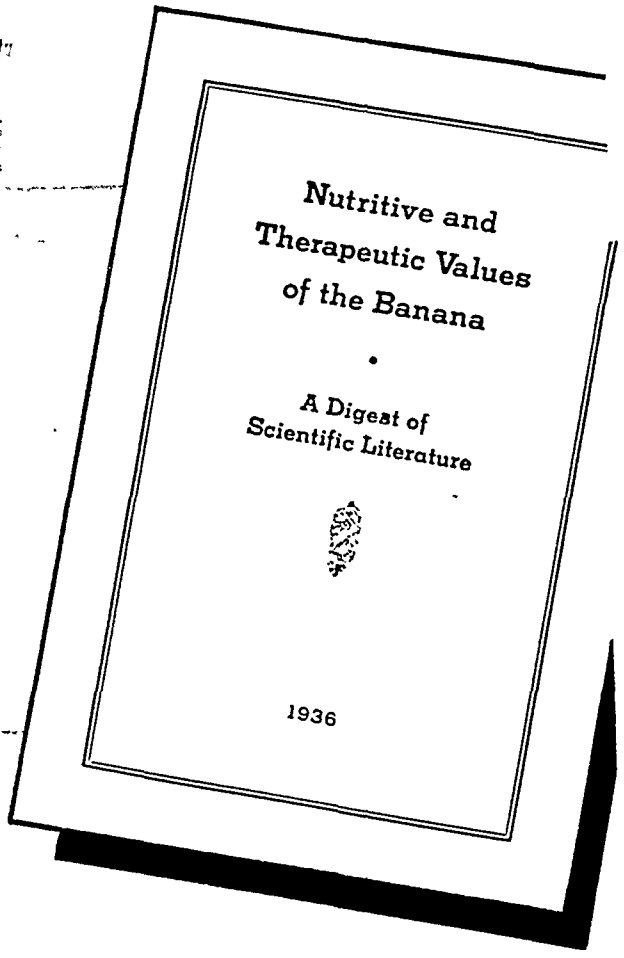


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accurate or beneficial as evidenced by the variability in the time chosen by different surgeons. This article gives the result of a serious attempt to develop an organized routine post-operative study to determine the time for removal of the tube in any individual case. Some rather definite tests are described.

The food test which will result in increased biliary drainage after meals if the sphincter of Oddi does not show normal physiological relaxation is a much safer test than the frequently-used one of clamping off the tube for a period of time. Drainage, of course, must be continued until satisfactory relaxation occurs. Daily microscopic examination for pus cells is of value—drainage obviously being required as long as more than an occasional pus cell is found. A study of the crystals present in the bile sedimentation is of importance. Fragments of cholesterol crystals are strongly suggestive of the presence of a stone remaining in the duct. Calcium crystals are usually indicative of an associated pancreatitis which would be an indication for farther drainage. Any appreciable quantity of calcium bilirubinate crystals indicate a continuation of pus and a colon bacillus infection. The tube in these cases should not be removed at the disappearance of pus, but not until a marked decrease in these crystals occurs. The presence of large amounts of pancreatic ferments is a contraindication to removal of the drainag etube since painful excoriation of the abdominal wall will rerult from contact with such bile. In some cases this is the result of an anatomical anomaly but will be taken care of safely if the sphincter of Oddi functions properly.

Although of no significance in determining the time for removal of the tube, a study of the bile salt output, in conjunction with the other examinations, will indicate, when a decrease occurs, the need for active liver therapy (glucose, sodium chloride, and fluids).

J. Duffy Hancock, Louisville.

SURGERY OF THE LOWER COLON AND RECTUM

JONES, DANIAL FISKE.

"Carcinoma of the Rectum and Colon." South. Med. Jour., 29:339-344, April, 1936.

This is an unusually practical paper based on a large personal experience. A plea is made for early diagnosis and emphasis upon the comforts rather than discomforts of colostomy. Change in bowel habit or sensation, bleeding from the rectum, and any other symptom referable to the rectum or lower abdomen should be considered due to carcinoma of the rectum or colon until proved to be otherwise. The most important symptom in carcinoma of the rectum is pain evidenced as an ache or tired feeling over the sacral area or discomfort in sitting. The other significant one is bleeding. Abdominal pain due to various degrees of obstruction is especially present when the growth is in the colon. Proper digital and sigmoidoscopic examination, both of which are described, should give a correct diagnosis in 100% of the cases of carcinoma of the rectum—X-ray examination in only 40%. Not much importance is attached to the usual text-book symptoms of constipation, diarrhea, ribbon stools, loss of weight, and the age of the patient.

The operation done should be an extensive radical one. Five different procedures are named and the abdominoperineal operation in one and two stages is described. Proper preparation of the patient is emphasized. This includes preliminary cecostomy, and glucose and digitalis where indicated. Ether is the anesthetic of choice. Temporary paralysis of the bladder is an annoying post-operative symptom. The great majority of men are impotent after the operation. Operation is definitely preferred to radiation. While the value of aseptic anastamosis is appreciated, more emphasis should be placed on the preservation of the blood supply and the prevention of intra-intestinal pressure. A dry colon is a much safer one to work with than is one containing liquid feces. Some interesting personal statistics are tabulated.

J. Duffy Hancock, Louisville.

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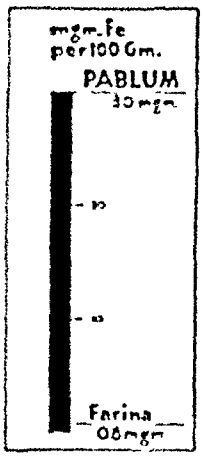
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President's Address*

By

HOWARD F. SHATTUCK, M.D.
NEW YORK, NEW YORK

IT has been a custom of this Society, for the President to address the Association at the beginning of each annual scientific session. First, I want to thank the Association sincerely for electing me your President last year. It is a great honor to be added to the long line of my distinguished predecessors. I also wish to express my grateful appreciation to the officers and members of the Council for all they have done to help carry on the work of the Association this past year. We are particularly indebted to our most efficient Secretary, Dr. Boles, for the great amount of time and thought he gives to our society's affairs. In addition to his many routine secretarial duties he has had the major part in arranging this year's program. I feel especially grateful to all our members for their continued interest and support which have made possible this year's promising scientific program.

I take this opportunity to extend a cordial welcome to our newly elected members, research, active and associate. The lengthening waiting list for membership makes your election at this time increasingly significant. The value and importance of this organization in its special field of medicine have been amply described by several of my predecessors in office. All the new members, I am confident, will share with the other members, a feeling of gratitude for the scientific inspiration and pleasant association that this society affords.

The addresses of former Presidents have so completely covered the general aspects of gastro-enterology and the affairs of our Association that there is little new to be said on these subjects. Then too, with such a profitable program awaiting us, I do not feel justified in delaying it with any extended remarks.

The American Gastro-Enterological Association, during its almost forty years of existence, has done much to develop the field of its special interest in America. A former President, Dr. Piersol, has well shown how gastro-enterology has become firmly established as a division of internal medicine of special interest and importance. During the period of its development there has appeared an increasing number of other medical specialties or subdivisions of internal medicine, if you will, such as cardiology, pulmonary diseases, diseases of metabolism, allergy, endocrinology and, more recently, hematology and arthritis, not to mention them all.

In recent years we have heard much about the necessity of intensive specialistic training and experience for men wishing to enter one of the medical or surgical specialties. We should continue to stress the equally urgent necessity, for those entering the medical specialties, of becoming and remaining competent and experienced internists. This applies particularly to the field of gastro-enterology. In fact, very many members of this Association are most competent and eminent internists with a special interest in gastro-enterology. Some of them prefer to be considered as internists solely and simply. This, of course, is not a new thought. Many of my predecessors have emphasized it in their introductory remarks. This is, I believe, what Dr. Samuel Meltzer had in mind when, as our President thirty-three years ago he said, "While there may be some doubts about the desirability of too great a division of labor in the practice of medicine, there can be no doubt about the desirability of the division of labor in the study of the science of medicine. If we build up this Association on a high, ideal, scientific basis and develop it along these lines we shall dispell distrust and attract the best workers in this field."

On this same point, in his Presidential address before the society, Dr. Piersol ably said, "The gastro-enterologist who is worthy of the name, must first of all be a thoroughly trained, broad-minded physician. This is one of the strongest arguments against men taking up gastro-enterology or any other special branch of internal medicine before they have received a broad, general medical training. It can be truly said that although a good internist may be a poor gastro-enterologist, a good gastro-enterologist must never be a poor internist."

In a symposium on abdominal symptoms at the Southern Medical Association, Dr. Thomas R. Brown aptly put the matter as follows: "Man is an entity, not a summation of his organs and his systems, however carefully each of these be studied separately. Add together the findings of an eminent specialist in every field and you will not get the clinical picture of the case, for the organism is not the mere sum of its constituent parts. To be understood it must be studied, *soma* and *psyche*, as a whole, for no two men are alike morphologically, physiologically or psychologically."

I need develop this thought no further. My plea is that we become as competent, skilled and experienced internists as we can, and that we strive to continue so. If at all possible we should continue to examine and treat patients with cardiac, pulmonary, blood and renal disease. I am sure that as a result we will give better, wiser and safer service to the patients we see in the hospital or in private practice. We shall likewise thus avoid the pitfalls of narrow specialization, or as someone has well put it, "of knowing more and more about less and less."

There are two practical steps we might take as an Association along these lines. First, in electing new, active and associate members, we can pay even more attention to the clinical qualifications of our candidates than we have perhaps in the past. In addition to requiring an interest in the aims and purposes of our Association, and contributions to the literature, could

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we not give added attention to the clinical training, ability, and skill of prospective members? Secondly, as has been suggested before, could we not include in our membership some outstanding, capable clinicians who have not necessarily written papers or done research? If we took these two steps, I believe our Association would increase its prestige, influence and usefulness.

Cholesterol Metabolism in Jaundice*

By

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STUDIES in cholesterol metabolism are becoming increasingly complex as the subject is explored by different investigators. The level of blood cholesterol is known to be affected by variations in the function of the pituitary, thyroid, gonads, pancreas and adrenals. Disturbances in blood cholesterol values have been reported in hypo- and hyperthyroidism (1), vitamin A (2), C (3) and D (4) deficiency, diabetes (5), tuberculosis, nephrosis and amyloidosis, fevers (6), epilepsy, pregnancy, liver disease, gall bladder disease, arthritis, leprosy (7), and arterioschlerosis. In addition, Berman (2) has called attention to a syndrome of asthenia and cholesterol deficiency which he terms *asthenia cholesteropriva.*

The relationship of cholesterol esters to total cholesterol has been thoroughly studied. The variations of the cholesterol—cholesterol ester ratio in disease, and particularly in liver disease have been described by Thannhauser and Schaber (9), Epstein (10), Laroche, Griant and Costes (11) and others. It is accepted that the esters are lowered in parenchymatous liver disease, but Hawkins and Wright (12) feel that this lowered ester ratio is not a valid index in differentiating obstructive from toxic jaundice. They point out, as have other investigators (11), that liver infection, superimposed on obstructive jaundice promptly lowers blood cholesterol and the ester ratio.

AUTHOR'S STUDY

The purpose of this paper is to demonstrate some of the changes that occur in liver disease in the level of the bile cholesterol and its relation to the blood cholesterol variations. Since all the cholesterol in bile is in the form of free cholesterol (13), no attempt has been made to include cholesterol ester determinations of the blood, and all figures for blood cholesterol refer to the total blood cholesterol. The procedure for blood cholesterol determinations was after the method McClure and Huntington (14). The bile cholesterol was determined by Bloor's (15) method. Repeated examinations on the same bile specimen showed results which checked within 10%, and this was felt to be sufficiently accurate for our purpose. All determinations were done at the laboratory of the New England Deaconess Hospital.

The determinations of bile cholesterol were made on "C" bile, bile obtained either by duodenal tube after the dark "B" fraction had been discarded, or bile obtained from fistula or from a T tube in the common duct after operation. The normal bile cholesterol is a somewhat variable figure, but we feel that any values between 20 mg. and 50 mg. per cent can be assumed to be in the normal range. McClure and Vance (16) find the average normal to be 25 to 48 mg. per cent.

Table I shows the variation of blood and bile cholesterol in *obstructive jaundice.* In some of these cases there was no jaundice and no elevation of blood bilirubin at the time these determinations were made. They were included in the series, however, because of other factors which made them of interest.

In those cases with long standing obstructive jaundice, bile obtained from the common duct within one or two days after operation shows a low cholesterol and the blood cholesterol is elevated (Cases 1, 2, 3). Case 3 had had jaundice for only eight days and the bile cholesterol is only slightly depressed; the blood cholesterol is normal. Cases of intermittent jaundice due to a common duct stone (Cases 4, 5, 6) showed a normal or an elevated bile cholesterol and a normal blood cholesterol. Case 7 had an external biliary fistula and a complete stricture of the common duct. Both the bile and blood cholesterol are normal, although there was no bile passing into the intestinal tract, and consequently no reabsorption of cholesterol from this source. This has been described as a conservative mechanism and necessary to preserve the normal balance of cholesterol in the body. Case 8 also had an external biliary fistula with intermittent jaundice. The blood bilirubin was normal at the time this observation was made. This case is interesting in that she had severe hyperthyroidism and this condition is reflected in the elevated bile cholesterol and the low blood cholesterol. Case 9 had gall stones and common duct stones but was not jaundiced. She had a severe spontaneous myxedema and showed a low bile cholesterol with a high blood cholesterol. After four months treatment with thyroid the blood and bile cholesterol figures are normal and her general condition had improved sufficiently to permit operation. The presence of the stones in the gall bladder and the common duct did not influence the cholesterol values.

In the *toxic jaundice group* are included two cases of unusual interest. Both were cases of severe toxic hepatitis, one of which recovered and the other died (Cases 10 and 11). The three determinations of bile cholesterol in the case which recovered gave low figures, while the blood cholesterol was elevated. The case who died showed a progressive fall in the level of

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TABLE I

Obstructive lesions

No.	Diagnosis	Date	Cholesterol mg. per 100 c.c. Bile	Cholesterol mg. per 100 c.c. Blood	Source of Bile	Remarks
1.	Carcinoma of Ampulla of Vater		7	308	T Tube, day after operation	Complete obstruction
2.	Common Duct Stones Chr. Hepatitis	12-6 12-18	6 54	216 158	T Tube, day after operation T Tube	Complete obstruction
3.	Common Duct Stones Stricture of Common Duct Chr. Hepatitis	2-10 2-28	16 19	182 138	Duodenal Drainage Pre-operative T Tube, post-operative	Partial obstruction Jaundice for 8 days
4.	Common Duct Stones	1-17 2-1	50 106	126 149	Duodenal Drainage T Tube	Intermittent jaundice Post-Op. Pneumonia
5.	Common Duct Stones	1-12 1-18 1-30	26 44 76	99 104 171	T Tube, one week post-op. T Tube T Tube	Intermittent obstruction Jaundice at operation
6.	Common Duct Stones Recurrent	1-30 3-12	104 97	150	Duodenal Drainage T Tube	Intermittent jaundice
7.	Stricture of Common Duct External Biliary Fistula		45	208	Bile from fistula	Not jaundiced
8.	External Biliary Fistula Common Duct Stricture Primary Hyperthyroidism		68	138	Bile from fistula	Not jaundiced
9.	Common Duct Stones Myxedema	12-18 4-1	9 48	358 180	Duodenal Drainage Duodenal Drainage	Thyroid medication for 4½ months, then operation

blood cholesterol over a twenty-four day period of observation. The last blood sample for a cholesterol was taken on the day of her death. Two attempts were made during her illness to obtain bile by duodenal drainage, but there was no bile in the duodenum. The one bile cholesterol determination was made on bile obtained from the common duct at autopsy and we were much surprised to find a bile cholesterol value of 54, more than twice the blood cholesterol figure taken only three hours previously while she was still alive.

Case 12 was a very severe toxic jaundice complicating ulcerative colitis. The one bile determination seemed to be all that the patient's condition would allow. His blood cholesterol was high (300 mg.) and the bile gave a low figure. Because of the high blood cholesterol we felt the prognosis in his case was better than the clinical condition seemed to warrant, and he justified this by recovering from the jaundice although he died some months later from his colitis.

Case 13 was an early catarrhal jaundice in a young girl. The jaundice cleared rapidly and because of the unusually high bile cholesterol we suspected hyperthyroidism. The low blood cholesterol is additional indirect evidence. She later became much more nervous and showed unmistakable signs of hyperthyroidism, but we were unable to get a metabolic rate determination to confirm the diagnosis.

In case 14 the diagnosis, confirmed at operation, was chronic cholangitis. The patient had had repeated attacks of painless jaundice following a cholecystectomy some months previously. There were no stones in the common duct, and no obstruction in the ducts or at the sphincter of Oddi was demonstrated. The duodenal drainage was done during one of the episodes of jaundice. While the bile cholesterol is low, the blood cholesterol is within the normal range.

In the previous cases we have mentioned the variations in blood and bile cholesterol due to thyroid dis-

TABLE II

"Toxic" disturbances

No.	Diagnosis	Date	Bilirubin in mg. per 100 c.c.	Cholesterol in mg. per 100 c.c. Bile	Cholesterol in mg. per 100 c.c. Blood	Source of Bile	Remarks
10.	Toxic Hepatitis	2-14	4.4			Common Duct at Autopsy	Died
		2-15	9.0		139		
		2-18	12.0		107		
		2-28	25.0		62		
		3-10	28.0	54	23		
11.	Toxic Hepatitis	1-5	10.5				
		1-7	8.5	4	278	Duodenal Drainage	Recovery
		1-15	5.1				
		1-25	3.2	6	288		
		1-31	2.5				
		2-10	1.0	18	260		
12.	Toxic Hepatitis Ulcerative Colitis		8.4	3	300	Duodenal Drainage	Recovery ? Hyperthyroidism
13.	Catarrhal Jaundice		3.5	97	140	Duodenal Drainage	Spasm of Sphincter of Oddi
14.	Chr. Cholangitis		1.5	4	194	T Tube	

ease. Hurxthal (1) has showed very clearly that the *blood cholesterol in hyperthyroidism* is lowered below its normal level and rises to normal as the disease is controlled. He has also shown that in myxedema the blood cholesterol is elevated, and has postulated the fact that if the blood cholesterol is not elevated, even though the basal metabolism be low, the condition is not one of clinical myxedema, and is not benefited by thyroid medication. In the course of these studies, duodenal drainages were carried out on several cases of hyperthyroidism and of myxedema.

TABLE III
Hyperthyroidism

No.	Cholesterol mg. per 100 c.c.		Remarks
	Bile	Blood	
1.	88	152	Before operation
2.	42	150	Before first stage
	90		Before second stage Severe Toxicity
3.	68	128	Before operation
	25	210	Six months after operation
4.	90	122	Before operation
5.	68	134	Before operation

Table 3 shows the bile and blood cholesterol values in a small series of proven cases of primary hyperthyroidism. Other studies, not included in these tables, demonstrate that the same ratio exists in adenomatous goitre with secondary hyperthyroidism. Note the lowered blood cholesterol values and the uniformly elevated bile cholesterol. After operation these figures return to normal (Case 3).

Table IV shows the reverse of the picture seen in *hyperthyroidism*. The blood cholesterol values are high and the bile cholesterol values are all much below normal. After a suitable period of thyroid medication these figures tend to return to normal levels. These statistics clarify the abnormally low and the abnormally high values found in some of the patients with various types of liver disturbances, associated with thyroid disease, and tend to confirm the statement of Stone (18) that the thyroid is the "master regulator" of cholesterol metabolism in the body.

COMMENT

In obstructive jaundice the general trend is toward an elevation of blood cholesterol so long as there is no superimposed liver infection. If the obstruction is complete and of long duration the bile cholesterol drops to a low figure, but if it is incomplete or intermittent, bile cholesterol is normal or only slightly below the normal level. As soon as infection supervenes, both the blood and bile cholesterol are depressed, and the degree of this depression is a fairly good index of the extent of the liver involvement.

In toxic jaundice these disturbances of cholesterol metabolism vary with the severity of the condition. So far as we may draw any conclusions from such a limited number of cases, it seems that the blood cholesterol tends to remain at or near the normal level in the less severe cases and such a normal level allows a better prognosis than a very low figure. On the other hand the bile cholesterol is depressed and shows little tendency to return to normal values for some time. In the one fatal case in this series, there was a steady fall in the blood cholesterol. We have no adequate explanation for the unusual finding of a high cholesterol content in the post mortem specimen of bile.

The role of the thyroid as a regulator of cholesterol values, both in the blood and bile, is an interesting one. Jaundice with greater or lesser degrees of liver damage is a not uncommon accompaniment of severe hyperthyroidism, and some speculation is permissable as to the part played by the thyroid in producing some of the variations seen in cholesterol metabolism in liver disease. As an hypothesis which remains to be proved, it may be suggested that there is a reciprocal relationship between the liver and the thyroid as far as their cholesterol regulating mechanism is concerned. If such a relationship exists, when the thyroid is diseased the liver then eliminates either an abnormally great or an insufficient quantity of cholesterol in the bile, and the balance is disturbed. When the liver is diseased, the thyroid is unable to preserve the normal ratio between the cholesterol circulating in the blood and the cholesterol eliminated by the bile. This usually results in an elevation of the blood cholesterol. But when the liver damage is severe, the mechanism is thrown so far out of balance that the synthesis of cholesterol is seriously interfered with and blood cholesterol falls.

SUMMARY

In obstructive jaundice blood cholesterol rises while bile cholesterol is normal or low depending on the completeness of the obstruction and its duration.

In obstructive jaundice with liver infection, both blood and bile cholesterol are low.

TABLE IV
Hypothyroidism

No.	B.M.R.	Cholesterol		Remarks
		Bile	Blood	
1.	—32	6	390	Spontaneous myxedema
2.	—38	6	446	Cretirism
			176	After Thyroid
			156	After Thyroid
	—2		146	One year later
3.	—24	18.5	236	Had been on thyroid for 2 years
4.	—24	9.5	358	Spontaneous myxedema Common duct stones
	—2	48.0	180	4 months on thyroid
5.	—39	14	314	Spontaneous myxedema
		38	115	2 months on thyroid
6.	—27	trace	455	Post-operative myxedema
	—9	16	182	6 months on thyroid
7.	—23	8.1	166	Total thyroidectomy for heart failure
	—22	14.0	177	Receiving ½ gr. thyroid daily

In toxic jaundice the blood cholesterol is normal or low depending on the severity of the disease. Bile cholesterol is uniformly low and remains low after the condition has apparently cleared up.

Hyperthyroidism causes an elevation of bile cholesterol approximately in proportion to the depression of blood cholesterol.

Myxedema produces a low bile cholesterol and a proportionate elevation of blood cholesterol.

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DISCUSSION

DR. ANDREW C. IVY (Chicago, Illinois): I think it is established both experimentally and clinically that in hyperthyroidism the blood cholesterol value is decreased; also, that in hypothyroidism, clinical or experimental, the blood cholesterol is increased. Experimentally, we are certain that various hepatic disorders lead to alterations in blood cholesterol, but, as Dr. Wilkinson has pointed out, this occurs, unfortunately insofar as the diagnostic value of blood tests are concerned, in other diseases.

In regard to the effect of the thyroid on the cholesterol output into the bile, I think Dr. Wilkinson's work is very suggestive to one working in the experimental laboratory. Insofar as I am aware, no one has administered thyroid extract to biliary fistula dogs to ascertain the effect upon the elimination of cholesterol in the bile, nor has anyone removed the thyroid gland from a biliary fistula dog.

If we had such results, I should be more willing to place importance upon the clinical findings of changes in bile cholesterol in the patients which Dr. Wilkinson has presented.

However, the idea of there being a reciprocal relationship between the thyroid and liver in the metabolism of cholesterol is very interesting, and I hope it will be studied further.

So as I know the physiology of the liver and biliary tract, the most serious diagnostic problem is the differentiation, particularly in the absence of the gall bladder, between an obstructive jaundice and intrahepatic jaundice. I say it is a serious diagnostic problem because if the patient has obstructive jaundice he should be operated, but, if the jaundice is due to an intrahepatic disturbance and not to an obstructive disturbance, then injury of the patient would be inflicted by an exploratory operation.

With the problem in mind, during the past year, we have been trying to find out if a study of serum phosphotase might help in making such a differentiation.

It would appear if Dr. Wilkinson's observations obtain on a large series of patients that we have the solution of this very serious diagnostic problem, namely, that in obstructive jaundice, pure and simple, we should find a high blood cholesterol. If the jaundice is due to some intrahepatic disorder the blood cholesterol should be low; or, if due to an infectious or toxic hepatic disorder in conjunction with an obstructive jaundice, then we should find a normal or low blood cholesterol.

Obviously, if this is borne out by experimental and clinical work, such will be a very important contribution. I hope that this investigation will be continued.

Dr. Wilkinson indicated that the cholesterol in duodenal fluid in obstructive and toxic jaundice is low. It is known experimentally that if we produce an obstruction, and it does not have to be a complete obstruction, a white bile, or a bile low in pigment is secreted, and when we analyze such bile for cholesterol, we find that it contains relatively little.

The same thing is true when we produce an infectious or a toxic jaundice. Such is at least true for a certain stage of toxic jaundice; whether it is true of later stages, when regenerative changes are occurring in the liver, I am not so certain. In interpreting and applying Dr. Wilkinson's results, I think we should bear in mind the fact that one may observe changes in blood cholesterol in conditions other than obstructive jaundice, and hepatic and thyroid disorders.

DR. ABRAHAM LEON GARBAT (New York City): The problem that Dr. Ivy has brought up, namely of having in jaundice some means to differentiate those cases that are surgical from those that are medical, has been a subject that my associate, Dr. Harry Jacobi, has been studying at the Lenox Hill Hospital for the last five years. We have tried the cholesterol method, we have tried the fibrin method and recently have studied the problem of the sugar tolerance curve as a method for separating the toxic medical jaundice cases from the obstructive surgical ones.

We give our jaundice patients 100 grams of glucose on an empty stomach. We examine the sugar content of the blood before the sugar intake and again three-quarters of an hour after and again two hours after. We found very striking curves.

(Slide) The cases of toxic jaundice (catarrhal, acute yellow atrophy, arsenic, etc.), show a curve which begins at a fairly normal level and remains at a fairly normal level at ¾ hr. and 2 hrs,. or rises abruptly in ¾ hr. and comes down again in 2 hrs. The first occurs in the more severe toxic cases,.the latter in the less toxic. These curves are uninfluenced by the degree of jaundice as estimated by the icteric index.

In the cases of obstructive jaundice (obstructive either in the common bile duct as due to stone or stricture, or from obstruction at the head of the pancreas, or the intrinsic hepatic group of obstruction caused by cirrhosis or carcinomatosis or abscess) we found an ascending type of curve; *i.e.* the blood sugar at the end of ¾ and 2 hrs. continues to go up and does not come down. It makes no difference whether the fasting blood sugar is within the normal limits or higher than normal, the ascending nature of the curve is the same.

DR. SIEGFRIED J. THANNHAUSER (Brookline, Boston, Massachusetts): It has been about 13 years since my coworker, Schaber, and I described the relation between cholesterol and cholesterol esters and the fact that this ratio is changed in liver diseases. The investigation was based on a series of experiments on cholesterol balance. We thought at this time that the intake of cholesterol and the output of cholesterol could be balanced in determining the cholesterol content of the food and the output in the feces.

This idea with reference to a complete cholesterol balance is unrealizable. My former collaborator, Berta

Ottenstein, showed that cholesterol is destroyed and disintegrated by bacteria in the bowels. It is not widely known that cholesterol molecules are synthesized in the body, but body functions cannot destroy the cholesterol molecule. However, cholesterol is easily destroyed in the bowels by colon bacilli. The bacilli destroy what the human body cannot do within its intermediary metabolism. The same situation exists in uric acid metabolism. The body is able to synthesize the purin ring but cannot split off the ring system.

In view of this fact, the very interesting findings of Dr. Wilkinson who compares cholesterol concentration in the blood and the cholesterol in the bile may not have in every case but one meaning. According to the fact that bacteria destroy cholesterol, a decrease of cholesterol in the bile could be produced by bacterial action in an infected gall bladder.

Another thing that I would say is about the influence of thyroid on the cholesterol excretion. Cholesterol is excreted by the bile and, to a large extent, by the intestines as Zenke and I showed in bile fistula experiments. Thus the relation between bile cholesterol content and blood content moves not in a single track. There is a very important way of excretion to the bowels where greater amounts of cholesterol are excreted. Studying the influence of thyroid medication upon cholesterol output the cholesterol values should be compared not only from blood and bile but, of course, the cholesterol output in the bowels must be considered. In the bowels, however, cholesterol is disintegrated by bacteria so that we cannot attain a real and complete cholesterol balance which will show the effect of a medication on cholesterol output.

Nevertheless, Dr. Wilkinson showed an interesting way to approach the question of cholesterol metabolism.

DR. CARL H. GREENE (New York City): This study by Dr. Wilkinson is very interesting, though it is unfortunate that more reference was not made to the relation of the gall bladder to this picture. It is well recognized that gall bladder bile is more concentrated than hepatic duct bile but in addition the cholesterol is very much more concentrated than are the other constituents. Dr. Wilkinson has tried to eliminate the gall bladder effect.

On the other hand, the study of a series of cholecystectomized patients shows that after cholecystectomy, the bile remains dilute, and the cholesterol is low in the patient with no symptoms in whom there is no residual stasis in the common duct. If there is stasis in the common duct after cholecystectomy, then one may get dark concentrated bile on duodenal drainage.

In such patients, the cholesterol in bile from the common duct increases markedly. Under these conditions it is suggested that the common duct takes over the concentrating function that formerly was possessed by the gall bladder.

Strikingly enough, in Dr. Wilkinson's chart, the cases where the bile cholesterol was high were associated with gall stones in the common duct. Before his results are accepted unequivocally we must be sure that this accessory effect of stasis in the common duct and change in the function of the common duct epithelium is considered.

DR. S. ALLEN WILKINSON (closing the discussion): I wish to thank the speakers for their comments.

Dr. Thannhauser mentioned the fact that infection of the bowel may change the biliary content of cholesterol. That, of course, probably does take place, but in those cases which were obviously infected and in those cases where there was no infection that we could demonstrate, the cholesterol content of the bile was approximately the same.

Dr. Greene raised the question of the content of the cholesterol of gall bladder bile as compared with cholesterol in liver bile. We carried out cholesterol determinations on the "B" bile, or gall bladder bile, and found that it was approximately twice that of "C" bile. Those results are not included in this paper.

It seems unlikely that the presence of the gall bladder can greatly alter the concentration of cholesterol in the liver bile, since we found approximately the same values of liver bile cholesterol in those cases who had had their gall bladders removed or who had an external biliary fistula as we did in those cases where the gall bladder was present.

Biliary Stasis*

By

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THE development of the modern point of view regarding the treatment of diseases of the gall bladder has passed through several stages. Initially came the recognition of the possibility of surgical intervention, the development of the necessary surgical technique and the establishment of the superiority of the operation of cholecystectomy over cholecystostomy. Numerous surgeons have reported surgical statistics showing the almost uniformly good results obtained by cholecystectomy in cases of acute cholecystitis and of chronic cholecystitis with stone.

The extensive study of diseases of the gall bladder stimulated by these observations led to the recognition first, of the fact that many patients with chronic digestive ailments suffer from a chronic cholecystitis without stones, and second, that in such patients the results of cholecystectomy are often disappointing.

Three factors, metabolic disturbance, infection and biliary stasis, are generally accepted as of prime importance in the development of cholecystitis or cholelithiasis and the production of the associated symptoms. The relative importance of each is by no means established. The typical biliary colic usually is indicative of gall stones but the pathologists have empha-

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sized the frequency of "silent gall stones." Many patients with non-calculous disease complain of colic. While disturbances in cholesterol metabolism are cited to explain the origin of cholesterol calculi, they do not explain the associated symptomatology. Apart from biliary colics, the chronic indigestion which Monyihan long ago described as the inaugural symptom of gall stones is now generally ascribed to an associated cholecystitis and so to infection.

The *rôle* of infection in chronic gall bladder disease is obscure. Rehfuss and Hanssen and Yurevich have reviewed this literature within the past year. They pointed out the relatively small proportion of cases in which evidences of infection in the gall bladder or its contents can be demonstrated by bacteriological methods. Andresen explains this discrepancy as due to the fact that the gall bladder inflammation is only a part of a general chronic infection of the whole gastro-intestinal tube and its appendages. He stresses the importance of coincident infection of the stomach, duodenum, liver, pancreas, appendix and colon.

Other investigators, as Jones, have shown that many of the sensations, nausea, vomiting, distension and the like, of which these patients complain, can be duplicated by inflation of a balloon in the duodenum. The symptoms of the patient with cholecystitis therefore are explained as due to interference with the normal motor function of the pylorus and duodenum produced by reflexes arising in an inflamed gall bladder. Still another alternative is the view recently discussed by Ivy that this same symptomatology may be produced by stasis within the gall bladder or bile ducts as a result of disturbance in the normal motor function of this viscus, the so-called "biliary dyskinesia."

Biliary stasis alone is insufficient to produce calculi, and calculi have been observed under conditions which seem to preclude the presence of stasis. Stasis, however, serves to provide a favorable environment for the deposition of calculi and so augments the effects of associated infection or metabolic disturbance. The importance of such stasis has not received due recognition in the past.

A consideration of the factors controlling the filling and emptying of the normal gall bladder and of the possible disturbances therein has indicated that at least three types of disturbances productive of stasis and an associated symptomatology can be recognized clinically. These types are of importance both in diagnosis and treatment.

1. Obesity and a loss of muscle tone is observed in many women as the menopause is approached. Numerous observers and, most recently Alvarez and Vanzant, have emphasized the increasing proportion of cases of achlorhydria that are observed in older people. The presence of acid chyme in the duodenum not only causes a relaxation of the sphincter of Oddi but stimulates evacuation thus resulting in distension of that viscus. This may be referred to as an *atonic distension*. The resultant biliary stasis is signalled clinically by epigastric or hypochondric soreness or distress which is most marked during fasting. Colics are very infrequent. Achlorhydria or hypochlorhydria is shown by gastric analysis. Gastro-intestinal roentgenograms are usually normal. The shadow of the gall bladder in the cholecystogram is distended and atonic may show delay in either filling or emptying. Duodenal drainage may procure a large quantity of concentrated bile but frequently this is secured only after stimulation with olive oil. The biliary stasis is further shown by the presence of crystalline sediment. Such cases respond to therapeutic management with a stimulating diet and the administration of hydrochloric acid, a fatty diet or of olive oil between meals to stimulate evacuation of the gall bladder.

2. It has long been known that in a number of cases of duodenal ulcer the symptoms are those of gall bladder disturbance. In a further number of cases roentgen study of the gastro-intestinal tract shows a duodenitis, periduodenal adhesions, pylorospasm, gastric ulcer or the like, in association with disease of the gall bladder. In such cases it can be assumed that the increased motility and tone of the duodenal musculature and sphincter of Oddi interfere with the normal evacuation of the gall bladder. Because there is an increased resistance to its emptying, the gall bladder becomes distended and hypertonic. This may be refered to as a *hypertonic* or *spastic distension* of the gall bladder. Clinically it is characterized by frequent attacks of colic which may be accompanied by jaundice. Gastric hyperacidity usually is present. Roentgenograms of the gastro-intestinal tract show evidences of pylorospasm and spasm, hypermotility or increased tonus of the duodenal musculature. Cholecystograms show the gall bladder to be distended and hypertonic. Duodenal drainage shows evidence of stasis in the frequency in which concentrated bile is procured only after stimulation with olive oil. The bile is dark and concentrated and the presence of crystalline sediment is further evidence of the stasis. Such cases respond to therapeutic management with diets of the modified ulcer type, antispasmodic drugs such as belladonna, and alkalies to control the hyperacidity.

3. The association of symptoms of gall bladder disease with neuroses of various types is no new observation. The association of chronic appendicitis, a spastic colon, pelvic disease or pregnancy, with exacerbations of the symptoms of biliary stasis has been explained on a reflex basis. In such cases it may be assumed that there is a spasm of the sphincter of Oddi as a result of vagal stimulation which may arise directly in the central nervous system or reflexly in some other portion of the abdominal cavity. This spasm or increased tonus of the sphincter of Oddi interferes with the normal evacuation of the gall bladder which then becomes distended. This may be referred to as a *neurogenic* or *vagotonic distension* of the gall bladder. The resultant biliary stasis is characterized clinically by the presence of psychogenic factors or sources of reflex irritation which may explain the vagotonia. Biliary colic and even jaundice may occur. The gastric acidity is usually within the normal range and gastro-intestinal roentgenograms do not show evidences of local lesions in the stomach or duodenum. Cholecystograms show the gall bladder to be distended and hypertonic. Duodenal drainage shows evidence of stasis in the concentration of the bile and the presence of crystalline sediment. Concentrated bile, however, is usually obtained after stimulation with magnesium sulphate solution. Such cases respond to therapeutic management with change of environment, mental rest, sedatives, anti-spasmotics, and saline cathartics. It is this group in particular that is responsible for the vogue of "spa" therapy in the treatment of cases of chronic cholecystitis.

The evaluation of the exact *rôle* of the individual factors mentioned in the production of gall bladder

disease is difficult but the concept of biliary stasis explains many of the clinical features of this disease. Failure to correct the stasis is responsible for many of the cases of recurrence of symptoms following cholecystectomy. Biliary stasis, however, is not a single disease entity but may be the result of various types of disturbance in the motor activity of the gall bladder and biliary tract. These three main types at least can be recognized. The recognition of these types permits both a more accurate diagnosis and a more specific and satisfactory therapeutic management of the individual patient.

DISCUSSION

DR. CHARLES GORDON HEYD (New York City): The authors make positive statements and submit them to a critical analysis. They say that the *rôle* of infection in chronic gall bladder disease is obscure. That is not so. You might just as well say that because a man was shot through the chest with a bullet and you failed to recover the bullet, therefore you cannot interpret the damage. You can interpret the damage of infection in gall bladder disease irrespective of the finding of the bacteria.

After a consideration of the factors controlling the filling and emptying of the gall bladder the essayists allege that variations in these factors, with stasis, produce three types of gall bladder disturbances with a symptomatology that can be clinically recognized.

This morning I have put all of their descriptive terms into parallel columns. All of these gall bladders were distended. The first is called hypertonic or spastic gall bladder distention. The second is a vagotonic gall bladder distention and the third is an atonic gall bladder distention. The first group is based on the major pathology of the duodenal tract—ulcer, duodenitis, diverticulitis. The second group is based upon pathology in the colon, chronic appendicitis and pregnancy. While pregnancy without the benefit of clergy may be associated with nervousness and apprehension, its etiology is not neurogenous.

In all three groups, the X-rays showed filling delay of the gall bladder; the "drainage" all showed concentrated bile after olive oil, or concentrated bile after magnesium sulphate, and all showed crystalline sedimentation.

I submit that the designation of these conditions has not been proved and that the descriptions are interesting, if true.

These statements do not militate against the *rôle* of stasis in gall bladder disease. At what point does physiological stasis become pathological? That is the question! To lug in a duodenal ulcer, duodenitis, chronic appendix, pregnancy, pelvic pathology and say that these conditions produce three types of gall bladder disease, each with a definite pathological and clinical symptomatology, I think is straining far beyond even the erudite resources of chemistry.

The Treatment of Acute Hepatic Insufficiency and its Relation to Prognosis*

By

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THE difficulties that surround the making of an accurate prognosis in patients suffering from severe liver disease are still extremely great. It is with this in mind that a review is made of 83 cases of severe liver insufficiency. Comments on clinical and laboratory findings and their relation to prognosis and treatment will be presented.

Fifty-six cases taken from the records of the Massachusetts General Hospital since the year 1922 were considered as being of sufficient severity to warrant a diagnosis of acute liver insufficiency. In many instances the diagnosis of acute yellow atrophy was made and substantiated by autopsy. As far as one can judge by clinical and laboratory methods, the individual cases did not vary greatly in severity during the different years. An additional group of 27 patients, all of whom had liver insufficiency of a somewhat less degree, but associated with a known cause, are included for comparison. The term "acute yellow atrophy" in reality describes a histological picture, an end process of severe liver disease due to one of many causes and in that sense is not a clinical entity. It is for that reason that the term "acute liver insufficiency" has been employed in this discussion.

The group of 56 patients whose findings are given below practically was unselected. It includes cases of alcoholic cirrhosis, toxic cirrhosis, "catarrhal" jaundice, arsenical jaundice, cinchophen jaundice, jaundice following severe sepsis, a certain number without any known cause but presenting extreme liver insufficiency, and a small group associated with cholelithiasis and severe obstructive jaundice. (Table I). All of these patients had in common the finding of intense jaundice and all were so critically ill that survival was problem-

TABLE I

Cases of acute liver insufficiency

Diagnosis	No. of Cases	Deaths
Alcoholic Cirrhosis	11	8
Toxic Cirrhosis	4	4
Acute Yellow Atrophy		
Cause Unknown	16	14
"Catarrhal Jaundice"	6	2
Arsenic	4	3
Cinchophen	7	6
Sepsis	3	2
Gall Stones With Obstruction	5	4

*From the Medical Clinic of the Massachusetts General Hospital and the Department of Medicine, Harvard Medical School, Boston.
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atical in each instance. As a measure of the severity of each case attention has been paid to the intensity of the jaundice, enlargement of the liver and spleen, the presence of ascites, edema and purpura. Laboratory findings that were particularly noted included quantitative bilirubin determinations, dye retention tests and a search for occult blood in the stools. Other laboratory determinations were made on many of the patients but will not be discussed in this communication.

It is of interest to note that of the 10 patients seen between 1922 and 1925 there was only 1 survival. Of the 14 patients seen between 1926 and 1929, all died. The average mortality of these eight years is 95 per cent. In the past six years, 32 additional cases have been followed with 20 deaths, a mortality of 63 per cent. (Table II). The striking difference between the mortality of the past six years and that of the preceding eight years is sufficiently great to warrant discussion in spite of the relatively small number of cases.

In the hospital records one can note that between the years 1922 and 1925, treatment of these patients consisted mainly in the administration of a "low fat diet." This diet actually contained a relatively high proportion of carbohydrate but the emphasis was

TABLE II

Course of acute liver insufficiency

	No. of Cases	Deaths	Mortality	
1922-25	10	9	90%	95%
1926-29	14	14	100%	
1930-35	32	20	63%	
Entire Group	56	43	76%	

equally great upon the low level of fat. Glucose was administered by rectum in 3 cases and in very small amounts intravenously in 2 cases. During the next four years hospital orders were changed so that the patients were put on a "high carbohydrate diet" instead of a "low fat diet." It is difficult to determine the exact difference between the two diets but an attempt was made in the second four-year period to give the patient at least between 300 and 400 grams of carbohydrate a day. Four out of 14 cases received some glucose by rectal or subcutaneous routes and 4 had a little intravenous glucose therapy. In one case intravenous glucose was administered over a five day period. In the last six years the dietary treatment of all such cases has been that of a high carbohydrate diet and not infrequently an attempt has been made to give the patient 450 to 500 grams of carbohydrate by mouth. No rectal administration of glucose can be noted but 26 out of 32 cases received intravenous therapy with solutions of glucose ranging from 5 to 25%. In several instances intensive glucose therapy was not possible because of the short duration of the patient's hospital stay before death. There is little doubt that in this particular group of patients much more intensive glucose therapy has been attained in the past six years and it is of interest to note that at the same time there has been a marked decrease in mortality, a drop of about 30%. (Table III).

It is pertinent to inquire at this point whether the group of patients treated in the past six years represented patients who were less seriously ill than those seen in the preceding period. A review of the findings shows that the intensity of the jaundice was no greater in one period than another and an analysis of the figures in Table IV shows that in 33 patients quanti-

TABLE III

Treatment of acute hepatic failure

Time Period	Type of Diet	Rectal or Subpectoral Glucose	Intravenous Glucose	Mortality
1922-25	Low Fat	3	2	90%
1926-29	High Carbohydrate	4	5	100%
1930-35	High Carbohydrate	0	26	63%

tative van den Bergh determinations were made. Of these, 16 reached a jaundice severe enough to give a peak figure of over 20 mgm. per 100 c.c. The mortality of this group was 56%. Seventeen, or an essentially equal number, had a grade of jaundice which carried a quantitative bilirubin of under 20 mgm. per 100 c.c., although the jaundice was still intense and the mortality was 76%. In other words, in these severely sick patients the depth of the jaundice alone obviously is not of critical importance and does not seem to determine the prognosis in any given case. The bromsulphalein test was performed in 24 individuals, or nearly half the series. Eighteen of these had a dye retention of more than 50%, a figure that one could anticipate in view of the extreme degree of jaundice. The mortality in this group was 56%. The remaining 6 had a dye retention of less than 50% but still a relatively high figure, and 5 of these patients died, a mortality of 83%. It would appear therefore that the dye test as well as a determination of the intensity of the jaundice was by itself of little immediate prognostic significance. Inasmuch as the two tests usually sup-

TABLE IV

Relationship of jaundice to prognosis in acute hepatic failure

	Cases	Deaths	Mortality
van den Bergh Over 20 Mgm. Per 100 c.c.	16	9	56%
van den Bergh Under 20 Mgm. Per 100 c.c.	17	13	76%
Dye Retention Over 50%	18	10	56%
Dye Retention Under 50%	6	5	83%

plement each other this is a finding that might have been expected.

It has occasionally been noted by other observers that ascites and general edema may occur in acute liver insufficiency and such a finding is commonly looked for in chronic liver disease. It was somewhat of a surprise, however, to note that in this group of 56

patients at least 25 had demonstrable ascites and 26 had easily demonstrable peripheral edema. The author has commented on the prognostic significance of ascites and peripheral edema in a previous communication (1) and it is certain that they do not occur except in seriously ill patients. That they were as common as is indicated by these statistics has not been pointed out

TABLE V

Relationship between ascites and intravenous glucose therapy

	Deaths	Mortality
Patients with Ascites and I.V. Glucose		
11	7	63%
Patients with Ascites and No I.V. Glucose		
14	13	93%

in the literature. The number of patients showing ascites and edema was no greater in the years before 1930 than after this date and from this criterion alone it would seem that the two groups of patients under discussion presented no great clinical difference from the point of view of severity of the underlying condition. The mortality of all the patients having ascites was 80%, of those showing edema, 80%, and of those showing ascites and edema, 86%. In other words, the mortality of those patients showing such a serious finding was essentially the same as that of the entire group and it can therefore be said that ascites and edema while indicating severe liver insufficiency are not sufficient to be of absolute prognostic importance in any given case.

Of greater interest, however, is the fact that of the 14 patients who had ascites and no intravenous glucose the mortality was 93%. Of those patients receiving intravenous glucose therapy a much lower figure was obtained, namely 63%. This finding would seem to indicate again that the introduction of intensive glucose therapy by the intravenous route had a determining influence upon the favorable outcome in many of the cases. (Table V).

Although the number of cases observed is altogether too small to give more than an indication, it is of interest to note that of the 56 cases 7 showed purpura. All of these patients died.

In view of the high mortality noted among the few patients showing purpura it was thought advisable to see whether bleeding occurred in any appreciable degree from the gastro-intestinal tract. Of 39 patients the survival period was sufficiently long to permit stool examinations. 17 of these showed positive tests for occult blood with gum guaiac. 14 of these patients died, a mortality of 82%, which was that of the entire series and it would seem that there was no intimate connection between the appearance of purpura and the existence of small amounts of bleeding from the digestive tract. The finding of such a high percentage of strongly positive tests for occult blood was also of interest inasmuch as none of these patients had malignancy of the head of the pancreas or the digestive tract and such a finding therefore could not be taken as suggestive of the latter diagnosis. It is also obvious from the above that the presence of occult bleeding from the gastro-intestinal tract is not of absolute prognostic significance.

Study of the various therapeutic measures employed in this group of patients indicates that the main difference to be noted before the year 1930 and after that date lies in the fact that intensive intravenous glucose therapy plus the administration of as large quantities of carbohydrate by mouth as was possible have constituted the only change of importance. That intravenous glucose therapy contributed materially to a reduction in mortality in the condition under discussion would also seem to be a proper deduction. The findings in Table VI certainly suggest that the more intensive the glucose therapy the better the prognosis. It is possible that transfusions during the appropriate periods in the course of individual cases may prove to have been of real importance and observations on a few recent cases would seem to indicate that such a measure might prove of additional importance in critical cases. The use of diuretics or abdominal paracenteses constitute therapeutic measures calculated to give symptomatic relief only. The use of the former, however, is not always associated with satisfactory results and may prove quite disappointing.

In the most seriously ill patients it is obvious from the above data that neither specific clinical findings nor laboratory data can give the information necessary to determine the outcome in a given case. The finding of ascites, edema and purpura is undoubtedly of bad prognostic significance but it is undoubtedly true that such findings do not preclude a favorable outcome. In a previous article (1), the author has stressed the importance of a spontaneous diuresis as one of the most important findings from the point of view of prognosis. That this is true is evidenced from the findings in the cases under discussion. Satisfactory observations of fluid intake and output were made on 41 of 56 cases. In 9 cases, or 22%, a real spontaneous diuresis occurred during treatment. Of the cases in which this was noted all but one recovered.

For purposes of comparison there is also presented an unselected group of 27 cases characterized by acute or subacute liver insufficiency of a somewhat milder degree. In each of the cases the condition had been precipitated by a known liver poison such as arsphena-

TABLE VI

Mortality from hepatic failure in relation to duration of glucose therapy

Duration of Glucose Therapy	Dead	Living	Mortality
1 Day or Less	30	1	96%
3 Days or More	9	11	45%
5 Days or More	7	10	41%
10 Days or More	2	7	22%

mine. The chief clinical difference between this group and the preceding one lies in the absence of ascites, edema,* and purpura. The intensity and duration of the jaundice noted in these patients did not differ to any marked degree from those already discussed and certain laboratory tests apparently indicated as great a disturbance of liver function. That the hepatic dis-

* 2 had slight edema.

turbance was not so severe, however, is obvious from the fact that in this particular group there were no deaths. It is of some interest, however, that in two-thirds of these cases intensive glucose treatment by the oral and intravenous routes was carried out. It is of further interest that out of 21 instances where fairly accurate observations were made, a definite spontaneous diuresis was observed in 10 cases, or 48%. As already pointed out, I feel sure that the occurrence of such a diuresis is a sign of the utmost importance as regards immediate prognosis. It is rare indeed to have a patient succumb from acute or subacute liver injury, regardless of the cause, when such a finding has been noted. An excellent example of this fact may

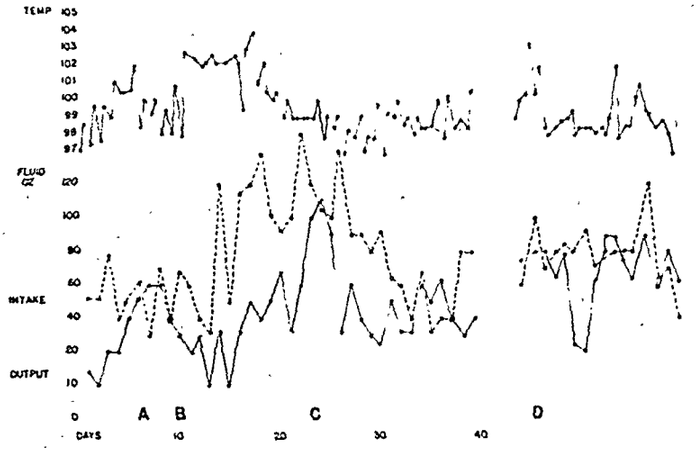


Chart 1. Course of hepatic insufficiency with special reference to urinary output. A. Striking clinical improvement with occurrence of a diuresis. B. Onset of erysipelas. C. Spontaneous diuresis with second period of improvement. D. Bronchopneumonia.

be found in the following case which was followed recently on the medical ward.

The patient, a man of 40 and a confirmed alcoholic, entered the hospital after a prolonged debauch, in obvious liver failure. Physical examination showed a large, obese individual with a coarse tremor such as is seen in delirium tremens. There was moderate icterus of the skin and sclerae, telangiectases on the face and prominent veins on the abdominal wall. The mouth was extremely red and the mucous membranes were dry. The liver was 3 fingers below the costal margin and the spleen was easily palpable. There was a small amount of ascites as evidenced by shifting dullness of both flanks. There was no edema of the extremities. Knee jerks were absent and the patient complained of numbness in the legs and feet suggesting a peripheral neuritis. During the next week his jaundice increased rapidly and the ascites became obvious to the point of distention which interfered with his breathing. There was an associated edema of the extremities.

The intensity of the jaundice waxed and waned throughout the three months in the hospital. The ascites tended to recur periodically after tapping. Laboratory data showed brown stools and a urine which was full of bile until the later weeks of his disease. The red count varied between 3,900,000 and 2,600,000, never going above the first figure in spite of nine transfusions. A quantitative van den Bergh test on admission showed 10 mgm., per 100 c.c., and reached a peak of 21 mgm. 11 days after admission. During the later weeks of the disease the van den Bergh dropped to a level of 3.5 mgm. Serum protein on admission was 6.5% but subsequently dropped to a level of 4.3% and has remained in that vicinity in spite of the numerous transfusions. A brief explanation of this low level can be partly supplied by the failure of the liver to maintain the serum protein and partly by permanent withdrawal of protein from the body associated with 12 abdominal paracenteses.

Intensive glucose therapy was instituted at once. This consisted almost exclusively of intravenous glucose. The patient was extremely difficult to manage until the later weeks of his disease and oral administration was almost impossible. Because of the obvious severity of the condition it was deemed advisable to give 25% glucose and this was carried out in almost daily injections in the past three months. After a stormy course, in which the jaundice gradually increased and ascites and edema, as well as marked mental symptoms, were striking features, there was a period of real improvement. This coincided with a diuresis, noted in the chart at A. Shortly thereafter (see B on Chart) the patient acquired a mild streptococcus infection of his throat. Facial erysipelas followed with increasing general symptoms such as deepening jaundice and delirium and an associated oliguria. At point C on the chart an increased urinary output was noted and again clinical improvement occurred. Two weeks later a further infection (see D on Chart 1) occurred with signs of a bronchopneumonic process at the right base. The patient managed to survive this further insult and again showed a striking increase in urinary output over that observed in the preceding week. From this point on improvement was gradual but continuous and the urinary output was high. It is probably important to point out that transfusions were given at almost ten day intervals, the indications being purpura, a persistent anemia, spontaneous nosebleeds, and a low serum protein. Belly taps were performed for relief of symptoms of distention. This case illustrates well the value of very intensive treatment in the face of the most severe grade of liver failure.

SUMMARY

In summary, we should like to stress the fact that in severe grades of liver insufficiency due to any cause there exist no laboratory or clinical tests that offer absolute prognostic information. Ascites, not previously existing, edema, purpura and a mousy odor to the breath are important clinical evidences of the most severe grades of hepatic failure. Oliguria proceeding to anuria, is of the utmost importance as a bad prognostic sign. Laboratory data confirm but do not accurately measure prognosis. Even in the most severe grades of liver failure as evidenced by the above symptoms, survival with a subsequent high degree of recovery of hepatic function may occur if intensive treatment is instituted. The reduction of the mortality in such cases from over 90% to 60% is apparent and eloquent proof of this statement. Such intensive treatment primarily rests upon adequate glucose intake, preferably by the intravenous route. Such an assumption is borne out by the findings of Althausen (2), Banks (3) and others who have shown in animals that for given amounts of glucose, the administration by the intravenous route is associated with greater glycogen deposition in the liver than when it is administered by mouth. The amount of glucose to be administered depends on the actual need. In the most severe cases

periodic transfusions constitute an added therapeutic measure of great importance. Purpura, anemia, spontaneous hemorrhages, a low serum protein, or failure to improve or glucose alone are the indications for transfusion. The simplest and most valuable prognostic sign indicating a real improvement is the finding of a spontaneous diuresis. This may and frequently does precede any demonstrable change in other clinical or laboratory findings.

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DISCUSSION

DR. H. L. BOCKUS (Philadelphia, Pa.): Any contribution to the prognosis and therapy of this type of acute severe liver insufficiency is certainly and decidedly worth while.

I do not think that any of us will disagree with Dr. Jones concerning the serious prognosis in those cases that show an acute edema and acute ascites. I was particularly interested in his comments on purpura. I believe he reported the occurrence of purpura in seven of these acute cases. I have lost two cases, within the past year, who developed a generalized purpura. I would like to ask Dr. Jones whether he has tried Vitamin C intravenously in any of these cases of acute hepatic insufficiency with purpura. I mention that because we have had some rather startling results in Philadelphia in the last few months with Vitamin C in purpura not associated with hepatic insufficiency.

Certainly the development of oliguria and anuria is a very bad prognostic omen. Nor do I think we can differ with Dr. Jones in his mention of the lack of prognostic importance of the serum bilirubin level in jaundice. It could not be expected to be of very much prognostic value.

I am sorry that Dr. Jones did not give us the benefit of his experience, which I am sure has been extensive, with certain other liver function tests in this group of cases from a prognostic standpoint because no one person sees a tremendous number of these cases in any one year. I think if we could group our information on this score it might prove of some value.

In collaboration with Dr. Tumen, I have been going over all of our cases of severe liver disease, not all of them acute, comparing the serum protein level with the various liver function tests. Twelve of the cases in this group were acute hepatocellular jaundice. They were not all of the severe type of insufficiency that Dr. Jones reports. I will give you the benefit of our findings in the serum protein levels in those cases.

The albumin was under 3.6 in seven of the acute cases, and the globulin was over 2.5 in six. The albumin-globulin ratio was less than 1.5 in nine. Three of those patients died, two of them had a serum albumin of less than 2.9 and two of them had an inversion of albumin-globulin ratio. In our experience in the diagnosis of the toxic type of acute liver disease, the galactose retention and possibly a measure of dye retention in conjunction with the serum bilirubin are superior to the serum albumin level. We have had insufficient experience in the acute cases with these particular tests to say anything about them prognostically. I should like to hear of Dr. Jones' experience.

It is interesting to be able to discuss Dr. Jones' paper in conjunction with the first paper by Dr. Wilkinson, a very important contribution to the subject. Dr. Wilkinson mentioned particularly the diminution in the total blood cholesterol, and particularly in the esters in the acute toxic jaundice. A good many European writers have stressed that point. We have been paying particular attention to it for several years. I must say that we have been rather disappointed in our results. It is true that occasionally we found quite a marked lowering in the blood cholesterol in the acute cases. We have seen a great many cases that were definitely hepatocellular in which the cholesterol level was not decreased but increased. I feel that the degrees of concomitant obstruction which is bound to occur in many of these cases must influence the cholesterol level. I wonder what Dr. Jones' experience has been in that regard?

The point of his paper is this, that parenteral glucose should be used in the treatment of acute hepatic insufficiency. I should like to ask Dr. Jones whether he thinks insulin is of any help and also whether he feels that oxygen may not be of value in some.

I should like to stress particularly the necessity for giving the glucose continuously, having lost two patients with acute hepatic insufficiency in hypoglycemia within the past year. One developed an extreme hypoglycemia during the night. We thought we were watching the blood sugar level very carefully. In spite of frequent glucose infusions day and night, the glucose level was below 20 several hours before death. That patient had an acute yellow atrophy of streptococcal etiology associated with purpura developing during the puerperium.

It seems to me that the glucose should be given by the continuous drip method throughout the critical period of the illness. It is interesting, too, that Dr. Garbat's sugar tolerance curves have indicated that the body apparently needs glucose so badly. I was very much interested in his discussion of Dr. Wilkinson's paper because it fits in very nicely with our clinical experience with hypoglycemia in these severe and acute cases of liver insufficiency.

DR. CHESTER JONES (closing the discussion): The point that I was trying to make is what Dr. Bockus has already said, that these patients as a rule have been given up as moribund patients. The surprising thing is that no matter how well they are, no matter how serious the laboratory findings seem to be, a certain portion of them can be pulled through by rather heroic measures. It means, however, that measures have to be started at once and carried through.

These patients represent an excellent example in human beings of what Mann has produced in animals that are hepatectomized; they are getting along practically without a liver. The amazing thing is that one can carry them along by intensive treatment over a period of days or weeks and can rescue a certain number of them.

Purpura, I am sure, is a bad prognostic sign. We haven't tried Vitamin C, nor ascorbic acid in any of these cases. The number of tests that were tried on this particular group of patients under discussion was relatively few and we were trying to get an estimate of the value of two of the simple ones, namely, the quantitative bilirubin and the dye test. The important thing in these cases is to save the veins for intravenous therapy. Therefore, the number of tests that can be done is limited. Otherwise, if one keeps on doing tests one cannot treat the patient very well.

Determination of the serum protein does give an indication of the severity of the hepatic failure but the very fact that there is an edema or an ascites will tell you that the serum protein is abnormally low. One can estimate or guess that beforehand.

The galactose tolerance test has been done on a few cases, and in one or two such cases acute yellow atrophy was proven at autopsy. The glactose tolerance test was normal in both. It gives me little confidence in it as a test for immediate prognosis.

Cholesterol values do vary a great deal clinically. I think that any attempt to gauge the severity of a case and its prognosis by one or two determinations of cholesterol or cholesterol esters is of no greater value than an estimate based on one's own clinical experience in following these patients.

We have used insulin in a few cases. The patient I first referred to has had intensive glucose treatment for three months. The interesting thing is that he has hardly spilled over any sugar in the urine in spite of the very large amounts of glucose administered. At one period of the time in the hospital he was given insulin along with the administration of glucose. It did not materially affect the amount of sugar that spilled over in the urine. We could not see that there was any evidence that insulin really helped in the utilization of glucose.

We have used oxygen in one or two instances. In patients in as serious condition as these, it seems to me it is quite obvious that there may be, among other things, a partial oxygen lack and the use of oxygen may occasionally be of real help.

I also agree with Dr. Bockus that at times it may be wise to insert a cannula into a vein for continuous administration of glucose throughout 24 hours of the day, day in and day out, until one's patient is either better or worse.

Chronic Hepatitis with Jaundice (Biliary Cirrhosis)*

By

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and

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ROCHESTER, MINNESOTA

THERE is perhaps no more difficult diagnostic problem than that presented by the patient with jaundice of long standing, and certainly there is no condition in which efforts at treatment are less satisfactory. These patients often present the diagnostic criteria of what has been termed "biliary cirrhosis," that is, they have suffered for months or years from jaundice, intermittent pain over the region of the liver, pruritus, and digestive disturbances. On examination a symmetrically enlarged and firm liver, a splenic tumor, and factitious dermatitis from scratching are found; the biliary passages are patent, and the urine is stained with bile. From the standpoint of clinical symptoms and functional disturbances these patients present most of the characteristics of a chronic, and primarily intrahepatic, type of jaundice. Such cases of chronic jaundice are ordinarily grouped in the convenient catch-basket of "biliary cirrhosis," and thereafter the patients are treated only perfunctorily and with failure acknowledged in advance. One may borrow Corvisart's statement in regard to heart disease, when he criticized those who "looked on attempts at an exact diagnosis (in such conditions) as useless, because those diseases are incurable."

The term "biliary" in hypertrophic biliary cirrhosis implies that the noxious agent enters through the biliary ducts. This may be true of the obstructive cirrhosis and possibly in a small group of cases in which the condition is infectious in origin. However, in a large number of cases of chronic jaundice, as will be shown later, there is no evidence whatever of any obstruction or infection of the biliary ducts. Hanot's name has been associated with this condition. His thesis, published in 1875, was entitled, "Hypertrophic cirrhosis of the liver with jaundice." At this time there was still a great deal of argument as to whether or not this condition was a separate entity. Grossly, the essential feature was an enlarged liver, as contrasted with the small liver established by Laennec as characteristic of atrophic cirrhosis. Microscopically, the connective tissue infiltrated the lobules, as well as surrounded them, as it did in the atrophic form. German authors, however, continued to deny the existence of hypertrophic cirrhosis as a separate entity. There are today many authors who deny that hypertrophic biliary cirrhosis exists as a separate entity. Dr. W. J. Mayo pointed out the frequency with which chronic hemolytic jaundice and splenic anemia were confused with this condition, and Bloomfield, for example, omitted it from his classification of hepatic diseases.

Perhaps the term "biliary" should be dropped from descriptive terminology, unless it be restricted to cases of parenchymatous hepatic disease to indicate that chronic jaundice is a particular feature. This is in line with the idea of Rolleston and McNee, who expressed the opinion that there is a distinction between hypertrophic biliary cirrhosis and atrophic cirrhosis, and that this distinction is chiefly in the presence, in the former, of a chronic persistent jaundice. However, as they also pointed out, both conditions may affect the same patient, and the atrophic form may show many other features of the hypertrophic form, such as enlargement of the liver and spleen. In other words, the two conditions may not be distinct.

CLASSIFICATION

In a clinical consideration of chronic jaundice, it is first necessary to establish a tentative nomenclature and an arbitrary classification. We use the term "chronic hepatitis" only in its clinical sense, except in a few instances when referring to pathologic lesions; "cirrhosis" is used as a descriptive term for a more advanced process characterized by nodular hyperplasia, and "chronic atrophy" is used to describe a contracted and atrophic liver with degeneration of the hepatic parenchyma. The classification to follow is purely tentative and is intended primarily to avoid confusion; it is open to the objection of being based in part on clinical data and in part on pathologic findings. Chronic hepatitis with jaundice, therefore, can be classified as follows: (1) chronic biliary obstruction with resulting cholangeitis and hepatitis; (2) chronic infectious and toxic forms of hepatitis, including toxic cirrhosis;

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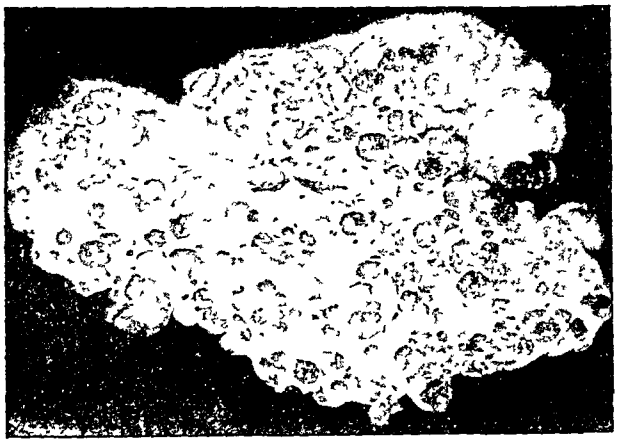


Fig. 1. Liver of a girl aged eleven years. Details are given in the report of Case 2. Liver weighed 711 gm. Dense fibrous tissue surrounding nodules of greenish or reddish tan color.

(3) chronic atrophy of the liver; (4) parasitic hepatitis; and (5) hepatitis secondary to familial bilirubinemia (constitutional hepatic dysfunction). This classification is by no means complete or inclusive, but it is at least possible to demonstrate examples of each of these types in a mixed group of cases of hepatitis with chronic jaundice and enlarged livers, as we shall show. For obvious reasons, we have omitted the pigmentary and syphilitic forms of hepatitis from consideration.

CHRONIC BILIARY OBSTRUCTION

The effects of calculous, cicatricial, and neoplastic obstruction on the structure and functions of the liver need no detailed consideration. It suffices to say that a considerable number of patients, who are, in reality, suffering from biliary obstruction, present themselves with a clinical picture that is difficult to distinguish from that produced by the infectious forms of hepatitis. The gross and microscopic appearance of the liver under these conditions is indistinguishable from that seen in supposedly primary types of cirrhosis, except for evidence of dilatation of the biliary ducts which indicates obstruction. Ductal and periductal inflammatory reaction from ascending infection may occasionally be present, but this cannot be demonstrated pathologically in many cases in which it is clinically suspected. Disorganization of the hepatic structure and portal obstruction may be sufficient to produce ascites, edema, and macrocytic anemia, which also are found in atrophic cirrhosis. The complete picture can be duplicated experimentally by ligation of the common bile duct of animals. In cases of obstructive cirrhosis, operation may be curative, even if the pathologic process is far advanced.

Following satisfactory removal of biliary obstruction, jaundice usually disappears, even if it has been present for a long time and extensive hepatic changes have taken place, however, a latent icterus and minor degrees of retention of bromsulphalein may persist for months or years after operation. Even in cases in which the liver has been damaged sufficiently to produce portal obstruction with ascites, patients may make a surprising recovery. An occasional case is seen in which the hepatic lesion progresses after operation. If obstruction cannot be relieved satisfactorily, as in some cases of extensive cicatricial contraction of the common bile duct, chronic jaundice may persist with associated ascending cholangeitis and hepatic enlargement and the terminal features will be those of ascending biliary infection, hepatic insufficiency, and cholemic bleeding. The obstructive cirrhosis that is secondary to congenital obliteration of the biliary ducts, choledochus cysts, and benign tumors of the biliary ducts may also be mentioned under this heading; because of the rarity of this type of cirrhosis no clinical description will be attempted.

There are certain rare cases in which there is a true cholangeitis and pericholangeitis, with a secondary hepatitis. The best clinical examples are seen following cholecystogastrostomy; diffuse hepatitis following this operation is by no means as common, however, as experimental studies would lead one to suspect. After cholecystogastrostomy, or after transplantation of the common bile duct into the intestine of the experimental animal, an ascending cholangeitis develops. Later, there is proliferation of connective tissue, and an inflammatory reaction with profuse lymphocytic infiltration about the biliary ducts. Miliary abscesses and a diffuse suppurative process are the usual terminal developments.

Diagnosis of these so-called obstructive forms of chronic hepatitis depends principally on suspicion, on signs of partial or intermittent biliary obstruction, and on the fact that hepatic functional tests frequently show more evidence of parenchymal hepatic damage than one encounters in the case in which nonobstructive hepatitis is of the same duration. Stone and stricture are the principal causes of chronic painless jaundice of this type; a neoplasm usually causes death long before the stage of cirrhosis is reached.

TOXIC AND INFECTIOUS FORMS OF CHRONIC HEPATITIS

When one eliminates patients who have obstructive forms of cirrhosis from a group of patients who have chronic jaundice, there remains a large and heterogeneous collection of patients whose hepatitis is believed to rest on a toxic or infectious basis. Just how the hypothetical toxins and bacteria reach and act on

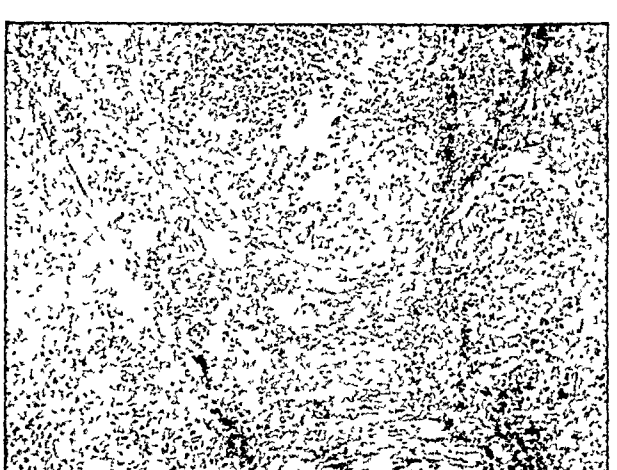


Fig. 2. Same case as that represented in Fig. 1. Extreme increase of connective tissue with collections of lymphocytes and adenomatous proliferation of liver cells. Complete disarrangement of normal structure.



Fig. 3. Liver; A, gross and B, microscopic. The patient was a woman aged thirty years. Jaundiced for two years. Liver enlarged. Serum bilirubin 12.5 mg. per 100 c.c. Death from intercurrent infection. Liver weighed 2682 gm. and was large and greenish, with finely granular surface and indistinct marking. Markedly swollen liver cells containing bile pigment. Slight increase in connective tissue which contained collections of lymphocytes and few polymorphonuclear leukocytes. Masses of bile in bile ducts.

the liver is largely a matter of conjecture. In the majority of cases the noxious agent probably reaches the liver by the blood stream. One school of thought holds that the effect is primarily on the supporting structure of the liver, which leads to an active proliferation of the connective tissue, a chronic interstitial hepatitis, which eventually affects the cells of the hepatic lobule. Epplen's excellent article pointed out the unlikeliness of this view. Another school holds that the effect of the toxin is primarily on the hepatic parenchymal cell, which undergoes degeneration or necrosis; acute yellow atrophy is a typical severe form. It is presumed that such toxins may be weak or strong, and may produce slight or extensive degeneration, which may vary from patchy to almost universal distribution. There may be single, acute episodes of toxic damage, which may recur frequently or may act for a prolonged period. As a result of the necrosis of hepatic cells thus produced, the lobule degenerates; if the subject survives, regeneration of the hepatic cells occurs. These changes are illustrated in livers affected by the toxic cirrhosis of Mallory, or "healed yellow atrophy" a term suggested by Wilson and Goodpasture. Bell said that it is very difficult, if not impossible, to distinguish this state from the ordinary atrophic cirrhosis. Many feel that this process of destruction and regeneration is the essential basis of all forms of parenchymal hepatic disease and that the different pathologic pictures are different stages or manifestations of the same process. Studies on experimentally produced hepatic lesions furnish strong support for this contention. Rolleston and McNee adhere to a course midway between the two schools of thought which have been mentioned; they maintained that the toxins also affect the supporting structure of the lobules, and produce active proliferation of the connective tissue as well as necrosis of the hepatic cells. The general trend of opinion, however, is toward the theory that the hepatic parenchymal cell is the primary site of injury.

In an endeavor to learn more of the clinical course and etiologic factors in the toxic and infectious types of chronic hepatitis and chronic atrophy, a series of fifty-three cases, in which chronic jaundice was not attributable to obstruction of the biliary passages, has been reviewed. There were twenty-three males and thirty females in the group of patients and their ages varied from eleven to sixty-seven years. In this group as a whole, the duration of jaundice varied from three months to nineteen years while in thirty-eight cases the duration varied from six months to five years. The degree of jaundice present was, as a rule, relatively slight, but an occasional case was encountered in which deep jaundice was present. In three cases in which there was deep jaundice, the process was relatively acute, but all three patients eventually recovered and are well some years later. In one case, intense icterus was a terminal development (icterus gravis); in another case it was of relatively long duration, and the patient died in one year from the beginning of the jaundice.

Pruritus, which was a common feature, was present in a high percentage of cases. It was absent in nine cases but in many cases it was the most prominent symptom and caused the most distress. Curiously enough, these patients presented relatively mild icterus, although in two cases in which the condition had been present for three and ten years respectively, there has been gradually deepening jaundice.

In a considerable number of cases, pruritus was the predominating symptom, with later development of melanosis, jaundice, and enlargement of the liver and spleen. Eight such cases were encountered in the group reviewed. Pruritus of three to five years' duration was present in five cases, it had been present for one year in one case, and for ten to twelve years in two cases.

In thirty-six cases, the liver showed marked enlargement which frequently extended to the region of the umbilicus. The liver usually was firm, smooth, and not definitely tender. The spleen was palpably enlarged in thirty-one cases, and in nine cases the enlargement was considerable. Ascites was a prominent feature in eight cases, although small amounts of free fluid were demonstrated in a number of others. In six of the eight cases, the ascites had been present for from three months to three years. All but one of the patients in these cases are known to be dead, and the sole survivor has required paracentesis regularly. In one case the



Fig. 4. Liver; A, gross and B, microscopic. The patient was a woman aged sixty-two years. Biliary colic four years before examination. Indigestion thereafter. Painless jaundice four months. Death from hepatic insufficiency. Liver weighed 1218 gm. Moderate increase of connective tissue with atrophy of parenchyma. Connective tissue increased, with collections of lymphocytes and bile ducts. Atrophy and fatty changes of liver cells.

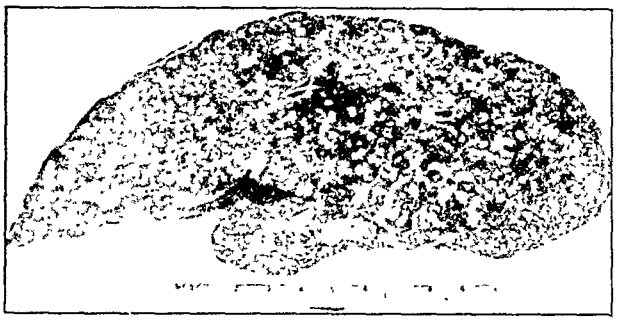


Fig. 5. Liver of a woman aged fifty-nine years. Jaundiced for five years. Ascites for six months. Serum bilirubin 5.8 mg. Death from hepatic insufficiency. Liver weighed 815 gm. and was moderately contracted and nodular with lighter areas of necrosis and darker areas of adenomatous proliferation.

ascites was present for six years before death. In one case the ascites, which had been present for four weeks, disappeared after the use of diuretics but recurred two or three times later. The patient in this case is now well. Of seven patients who had slight ascites, five are dead and the other two are well; one of the latter had been jaundiced for more than a year.

Melanosis was particularly prominent among the group who had pruritus; one patient presented almost a Negroid appearance. Osler mentioned a similar case in which the skin was "very bronzed, almost as deeply as in Addison's disease." In the whole group, melanoderma was present in eleven cases. In such cases, it is necessary to differentiate hemochromatosis, the pigmentation of chronic arsenical poisoning, and a simple melanosis, a point which is best settled by biopsy. Such a biopsy was obtained in nine of these cases; in two cases arsenic was demonstrated, and iron was present in one case. The remaining cases showed only excessive deposits of melanin.

Mild anemia frequently was present and macrocytosis was noted in twelve of nineteen cases in which blood smears were examined. Significant hemorrhage occurred in eleven cases; this apparently resulted from ruptured varices in six cases; in other cases a generalized hemorrhagic tendency was present.

Exploration of the abdomen was performed in twenty-seven cases; splenectomy was done in one case, omentopexy was performed in three cases, and exploration alone or with drainage of the gall bladder or common bile duct or with cholecystogastrostomy, was performed in the remaining twenty-three cases. In only one case of this group was any evidence of obstruction found in the common bile duct. The surgical procedures appeared to make little difference in the progress of the disease in those cases in which the patients survived. There were four postoperative deaths.

At operation the liver presented varying appearances. In the majority of cases it was much enlarged. In a few cases in which the condition was advanced, it was smaller than normal and presented a hobnail appearance. The consistency of the enlarged livers varied from normal to sclerotic; some were smooth, while others were granular or even nodular. In some cases the liver grossly appeared fairly normal, except for the increase in size. Occasionally it was described as appearing congested. The spleen frequently was found to be enlarged; in some cases the spleen was five times its normal size. The common bile duct usually showed little evidence of disease. Occasionally some enlargement of lymph nodes was found in the vicinity of the common bile duct. Biopsy of the liver was performed in five cases.

Twenty-four of the entire group are known to be dead, but more than 10 per cent of the original group are apparently well. The remaining patients continue to suffer from the disease; in some cases the disease has been progressive, but improvement has occurred in a few cases. The prognosis in the majority of cases does not appear to be encouraging.

In a search for etiologic factors in these cases, one meets great difficulties. Cinchophen was an apparent factor in one case. Alcohol possibly played a role in three cases; arsephenamine, in one; inorganic arsenic, in one; arsephenamine and alcohol, in one; arsenic and cholecystic disease, in two; and a combination of syphilis, arsphenamine, and cholecystitis, in one. One may take the following views as to the relationship of these hepatotoxic factors to the disease process; (1) that they are etiologic factors wholly or in part; (2) that they are not of etiologic importance but merely coincident findings; and (3) that the cholecystic disease is in some instances the result of the hepatic disease. There seems little doubt that inorganic arsenic, arsphenamine, and cinochophen are definite hepatic toxins. In three cases inorganic arsenic was a probable etiologic factor; at least, in these cases, chronic jaundice and hepatomegaly were associated with definite signs and symptoms of chronic inorganic arsenic poisoning. The case against alcohol is by no means conclusive. Experimental cirrhosis has not been produced with alcohol, yet fatty changes occur and render the liver more susceptible to other toxins. Clinically, alcohol appears to act in combination with other hepatotoxins.

Three cases were encountered in which some toxin incidental to pregnancy appeared to be a factor. In two of these, pruritus began in the course of pregnancy; in another, the patient had noted slight scleral icterus for one year prior to pregnancy. One of these patients died six months after delivery, as a result of continued jaundice and ascites; another patient who lived twelve years, suffered chiefly from pruritus and finally died of a gastro-intestinal hemorrhage. The

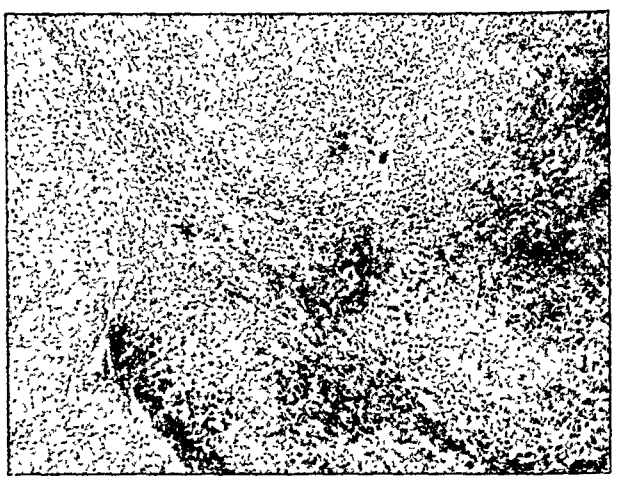


Fig. 6 Same case as that represented in Fig. 5. Increase of connective tissue trabeculae, bile thrombi, and areas of necrosis.

third patient continued to have symptoms for one year and then recovered. Ten years after recovery, she was enjoying excellent health. We have no records of necropsy in the two cases in which death occurred but the chronic nature of the disease assures a more extensive and chronic pathologic change than that seen in the usual toxemias of pregnancy.

Hepatic degeneration also occurs occasionally in the course of exophthalmic goiter, although in this series no such association was encountered. Neither did malaria and typhoid fever appear to be etiologic agents in any case in this series. No cases were encountered in which the disease began as an epidemic catarrhal jaundice, such as it did in those cases reported by Jones. There were no instances of splenic anemia in this series. One patient had an associated diabetes but there were no signs of hemochromatosis; in another case, in which there was cutaneous pigmentation, biopsy revealed iron in the skin.

Cases in which a definite infectious element seemed to play a part were of great interest. These may be considered under three groups: (1) those in which the disease involved the biliary tract primarily, with associated cholecystitis, cholelithiasis, and cholangeitis; (2) those in which there were associated systemic infections, and (3) those in which infectious processes were confined to the intestinal tract.

The first group warrants particular consideration, since cholecystectomy is frequently advised and carried out in such cases, with results that are usually unsatisfactory and not infrequently tragic.

There is much to suggest that long-standing biliary infection leads to serious hepatic damage. However, the hepatitis or cirrhosis may not be the result of biliary infection but may be primary, and the involvement of the gall bladder may be secondary. This was probably true in a number of cases in this series. It has been pointed out that clinically suspected cholangeitis cannot often be demonstrated pathologically in disease of the biliary tract, and it also must be acknowledged that the hepatitis described in association with cholecystic disease is often a purely local and superficial lesion which produces little effect on hepatic structure or function.

The importance of systemic infectious diseases, which was mentioned previously, has probably been underestimated. As pathologists have been pointing out for years, any severe infection leaves its mark on the liver; it is not uncommon to note extensive fatty change, focal necrosis, and other evidences of injury to the parenchyma. Whether such lesions lay the groundwork for the chronic hepatitis of later years is only a matter for conjecture; clinically, it does appear that infectious disease may initiate serious hepatic damage or provoke an exacerbation of a preëxisting hepatitis. In one case in the group studied, the hepatic disease apparently resulted from a severe systemic infection.

Chronic hepatitis may be associated with gastrointestinal disease of an infectious nature. We have recently observed two remarkable cases in which long-standing chronic hepatitis was associated with chronic ulcerative colitis; one of the patients in these cases had intractable diarrhea and anemia long before any signs of hepatic disease were present; in the second case, the time relations were less definite, but the colitis was clinically of some etiologic importance. In Case 1 it is possible that the achlorhydria permitted extension of the fecal flora as high as the duodenum, and permitted the occurrence of an ascending infection of the biliary tract similar to that which Hurst claims to be the most frequent mechanism of cholecystic disease.

Case 1. A man, aged thirty-one years, came under observation in March, 1936. Twelve years before he came to the clinic he had suffered from attacks of bloody diarrhea, which had lasted one to two weeks and had occurred two to three weeks apart. These attacks had occurred for one year; since then his bowels had moved five to six times daily, but with little distress or annoyance. Ten years before he came to the clinic, he had become pale. For five years he had noted a yellowish color of the skin, especially during summer months. There had been mild associated pruritus, which had persisted. Three years before he came under our observation, his condition had become so disturbing that he had consulted a physician. A marked anemia had been found. The value for the hemoglobin had been 40 per cent and the erythrocytes had numbered 1,500,000 per cubic millimeter of blood. Iron and liver had been prescribed, with marked benefit. In August, 1935, definite jaundice had been noted. He had not lost any weight and had not suffered any distress.

Examination at the clinic revealed that he was moderately jaundiced. The liver and spleen were slightly enlarged. The value for the hemoglobin was 15.9 gm. per 100 c.c. of blood and erythrocytes numbered 4,400,000 per cubic millimeter of blood. A fairly marked macrocytosis was present. Gastric anacidity was demonstrated. Roentgenologic examination of the esophagus, stomach, and small intestine revealed no abnormality, but roentgenologic examination disclosed slight mucosal changes throughout the colon. Proctoscopic examination revealed a granular mucosa that bled readily. The value for the serum bilirubin was 12.0 mg. per 100 c.c. The retention of bromsulphalein was grade 4. The result of the galactose tolerance test was normal. The excretion of hippuric acid was 4.86 gm. The value for the cholesterol was 463 mg. per 100 c.c. of plasma, and that for the cholesterol esters was 477 gm. per 100 c.c. of plasma. Bargen's diplostreptococcus was cultured from the stools, but could not be found in the duodenal contents. However, the latter contained Streptococcus faecalis. The diagnosis was chronic ulcerative colitis and chronic hepatitis with icterus.

After the cases in which the disease was of known toxic or infectious origin are excluded, there remains a group of equal or greater size, in which it was not possible to arrive at any definite conclusion as to the etiology. Indeed, Osler said that the absence of an etiologic factor was a remarkable feature of the disease. This is comparable with the situation in diseases of the kidney. There is considerable evidence to suggest that some metabolic disturbance may occur primarily, and produce fatty or other degenerative changes which render the liver susceptible to the effects of toxins or infections. As these cases are more thoroughly studied it may be possible to determine some definite etiology. Rolleston and McNee said that in some of these cases the disease may be the result of an ascending infection, but that in the majority of cases, like cases of scarletiniform nephritis, the condition is the result of hemic infection or intoxication of a chronic nature. Some of the cases undoubtedly belong to the group designated "toxic cirrhosis," and others are cases of chronic atrophy.

To summarize the etiologic findings in the group of cases in which chronic hepatitis is probably toxic or infectious in nature, one may say: (1) that there are cases in which a history of some chemical poisoning is obtainable, and in which the clinical picture in a

general way resembles that of the condition that has been designated as "toxic cirrhosis"; (2) that in other cases the disease appears to be of an infectious nature, the infection arising in the biliary or gastro-intestinal tract, or as a systemic infectious disease; and (3) that in a large group of cases the etiology is unknown.

PARASITIC HEPATITIS

The parasitic form of hepatitis with jaundice may be dismissed with brief comment. A diffuse amebic hepatitis is occasionally seen, but it is rarely characterized by jaundice or the development of cirrhosis. In the temperate climates, parasitic obstruction of the biliary ducts is chiefly of academic interest. Ascaris may invade the extrahepatic biliary passages and thus produce an obstructive type of cirrhosis. Clonorchiasis is responsible for diffuse hepatic damage, but this feature of the disease is overshadowed by the other manifestations. The diagnosis of these latter conditions is seldom made except at operation or necropsy.

CHRONIC ATROPHY

Occasionally, a patient is encountered who has slight but very chronic jaundice without other striking clinical features, except for hepatic enlargement. Such individuals may remain in reasonable health and the disease may show no particular progression for a long time (five to seven years in two of our cases); then, ascites, a hemorrhagic tendency, and hepatic coma may develop suddenly. The clinical course often resembles that of the toxic or infectious form of chronic hepatitis and the etiology may or may not be known. Clinically, the condition usually is diagnosed as biliary cirrhosis. The interesting feature of two of our cases was the pathologic evidence of a very chronic form of hepatic atrophy, which must have existed long before signs of hepatic insufficiency developed.

Case 2. A girl, aged eleven years, had suffered from fluctuating and entirely painless jaundice for seven years before she came to the clinic. For two and a half years a gradually increasing distention of the abdomen had been noted, and for a few months before she came under observation, impaired appetite, weakness, languor, and drowsiness had been conspicuous. Frequent epistaxis had been a late development. A diagnosis of Hanot's cirrhosis had been made by her family physician.

Physical examination at the clinic revealed that the patient was well developed and well nourished; she weighed 147 pounds (66.7 kg.) and her height was 64 inches (162.6 cm.). Moderate icterus and ascites were present; the liver was not palpable, but the spleen was easily felt. There was a slight edema of the ankles and clubbing of the fingers. The value for the serum bilirubin was 10 mg. per 100 c.c. and the van den Bergh reaction was direct. Retention of bromsulphalein was grade 4. The value for the hemoglobin was 11.5 gm. per 100 c.c. of blood and the erythrocytes numbered 4,150,000 per cubic millimeter of blood. A respiratory infection was followed by profuse bleeding from the mucous membranes, and by coma and death. Necropsy revealed a marked atrophy of the liver with very extensive adenomatous regeneration (Figs. 1 and 2).

It is well established that chronic atrophy and portal cirrhosis are really identical conditions. The curious feature of the cases which have been cited was the long continued and definite jaundice. The ascites and symptoms of hepatic insufficiency indicated an advanced lesion; this was confirmed pathologically. Numerous other cases of similar type were encountered in the group studied. The liver was not always enlarged but chronic jaundice was always present. Such cases as these suggest that the pathologic process is similar, whether jaundice is present or not, and that chronic hepatitis, with or without jaundice, in the final stages may progress to chronic atrophy. Deep icterus is seldom seen as a prominent symptom in the usual form of atrophic cirrhosis, except as Rolleston's "signal icterus" or in the terminal stages, although it may appear for brief periods in the course of the disease. Such episodes probably represent an acute process of hepatic degeneration and are often followed by anemia, edema, ascites, and other signs of increasing damage to the liver.

FAMILIAL HYPERBILIRUBINEMIA (CONSTITUTIONAL HEPATIC DYSFUNCTION)

For some years we have been interested in following the course of a group of individuals who have slight visible jaundice, an indirect van den Bergh reaction, and a slight but persistent hyperbilirubinemia, without definite evidences of hepatic disease or blood dyscrasia. For want of a better term, these conditions have been characterized as "constitutional hepatic dysfunction," the principal physiologic defect being a high hepatic threshold for bilirubin. That the hyperbilirubinemia is the result of hepatic dysfunction and not caused by an overproduction of bilirubin seems to have been well established by the work of Rozendaal, Comfort and Snell. As we will show later, this is the principal, if not the only, demonstrable functional disturbance in the presence of the milder degrees of chronic hepatitis. It, therefore, has not been surprising to find that in some of these cases in which the degree of hyperbilirubinemia has been minimal, definite signs of a progressive hepatic lesion and of disease of the biliary tract have developed with the passage of time.

In one case in which the condition had been present for a long time, mild jaundice was encountered; the value for the serum bilirubin varied from 3.3 to 6.7 mg. per 100 c.c. The van den Bergh reaction was indirect and the excretion of bromsulphalein was normal. An enlarged spleen was removed because of the possibility of an atypical hemolytic icterus; this did not produce any change in the patient's condition or in the degree of bilirubienemia.

THE CLINICAL COURSE OF CHRONIC HEPATITIS

In any group of cases of chronic nonobstructive jaundice, various stages of the disease may be present. In the majority of cases the condition is slowly progressive with gradually increasing icterus. In other cases the condition may progress more rapidly, with or without significant decrease in the size of the liver. If the patient survives long enough, chronic atrophy of the liver usually results. This is the usual course, but is more particularly true of the cases in which there are mild degrees of icterus. These cases, clinically and pathologically, resemble the usual case of portal or atrophic cirrhosis, except for the persistent jaundice. Improvement and apparently recovery occurred in 10 per cent of the cases in this series. In two cases in which the value for the serum bilirubin averaged 10 to 20 mg. per 100 c.c. for some months, recovery eventually occurred. In these cases the pathologic condition, perhaps, was subacute and the disappearance of the toxin probably permitted regeneration to occur.

Although symptoms are absent in some of these cases for a number of years, symptoms of chronic atrophy eventually develop. Long-continued jaundice which increases in degree and episodes of more intense jaundice or evidences of portal obstruction indicate a progressive lesion. In cases in which the disease is more chronic, ascites, particularly, indicates extensive disorganization of hepatic structure. However, in reviewing this group of cases we have been impressed by the fact that the patients live for a remarkably long time, many of them remained in an apparent stationary condition, clinically, for years. Thus, in one case, jaundice was present for ten years before the development of ascites, which occurred six years before examination. In other cases, progression may be extremely slow and pruritus may be the most significant symptom.

Case 3. A man, aged forty-one years, was seen at the clinic in 1925, 1931 and 1934. In 1921 he had had a two weeks' illness which had been characterized by jaundice. When he first came to the clinic he complained of pruritus, which had been present for nine months; he had lost 18 pounds (8.2 kg.). Examination at the clinic revealed a factitious dermatitis. The liver and spleen were only slightly enlarged. The value for the serum bilirubin was 2.2 mg. per 100 c.c., but the van den Bergh reaction was direct. The bromsulphalein test for liver function revealed a retention, grade 3. In 1931, his symptoms were improved. There was, however, some melanoderma and distinct jaundice; the value for the serum bilirubin was 5 mg. per 100 c.c. In 1934, his condition was somewhat worse than it had been previously; he had had attacks of epigastric pain with rigidity and tenderness. He had lost 10 pounds (4.5 kg.) and there was slight edema of the ankles. The liver and spleen were readily palpable. The value for the serum bilirubin was 10.7 mg. per 100 c.c. and macrocytic anemia was present.

The late complications arising in the course of chronic hepatitis with icterus are similar to those occurring in all chronic hepatic disease. These include evidences of portal obstruction, such as esophageal varices with or without rupture and hemorrhage, ascites, acute hepatic degeneration, icterus gravis, and hepatic insufficiency. The latter may be manifested by drowsiness, stupor, coma, convulsions, various reflex changes, hemorrhagic manifestations, evidences of renal insufficiency, and generalized edema.

TESTS FOR LIVER FUNCTION IN CHRONIC HEPATITIS WITH JAUNDICE

It must be admitted that tests for liver function are of limited value in cases of chronic icterus. The van den Bergh reaction is almost invariably direct, a fact which may be of importance in subclinical degrees of icterus. The quantitative determination of the serum bilirubin by this method gives further information. The value for the serum bilirubin was less than 5 mg. per 100 c.c. in twenty-three cases, 5 to 10 mg., in eighteen cases; 10 to 15 mg., in seven cases, and more than 15 mg., in five cases. In this series, the degree of retention of bromsulphalein was determined in thirty-seven cases. In all but four cases it was grade 3 to 4. In three of these four there was no retention after the patient had recovered from the hepatic injury. In the fourth case a very mild icterus was present and the van den Bergh reaction was indirect. Marked retention is to be expected in cases in which visible jaundice is present. There may be slight or moderate retention of dye after the value for the serum bilirubin has returned to normal in the process of recovery; at the onset of hepatic disease, the reverse situation usually obtains. Greene, McVicar, Snell and Rowntree have considered some of these tests in a previous article.

There is seldom any disturbance of the functions of the liver in regard to the metabolism of protein, carbohydrate, and fat, unless there be some complicating lesion such as diabetes mellitus or an episode of acute atrophy of the liver. Galactose tolerance tests were done on twenty occasions in sixteen cases, and in all but two instances normal results were obtained. In one of these cases, fatal hepatic insufficiency followed cholecystostomy; in the other case the patient survived exploratory laparotomy without difficulty.

The hippuric acid test (Quick) was done in seven cases; in only one case was it strongly positive and the

TABLE I

Hepatic functional tests in selected cases of toxic and infectious hepatitis

Patient	Serum bilirubin, mg. per 100 c.c.	Hemoglobin, gm. per 100 c.c.	Macrocytosis	Galactose excretion, gm.	Hippuric acid, gm.	Cholesterol, mg. per 100 c.c.	Serum protein, gm. per 100 c.c.	Albumin-globulin ratio	Takata-Ara test
La	2.6	12.1	+	8.64	4.72		7.7	2:1	Positive
Sh	12.5	9.12	+	Negative	4.19		6.78	1.16:1	Positive
Be	2.7	12.9		Negative	1.48		6.55	1:1.51	
Au	7.0	10.9	+	Negative	3.5	309			Positive
Re	4.2	12.6	+		3.99		6.7	1.40:1	
Ma	10.7	10.2				269	6.7	1:1.02	
St	2.5	13.3	0	Negative			8.08	1:1.59	
Wa	6.8	14.1	+	Negative	2.86		7.7	1:1.30	
Haz	12.0	15.9	+	Negative	4.86	463			
Ol	12.6	12.9		9.1 4.6		122	5.8	3.80:1	
Wo	3.3	16.4	+		5.4		7.0	2:1	Negative

patient in this case died soon afterward. Death also occurred in two of the cases in which the synthesis of hippuric acid was normal.

Macrocytic anemia is a common finding and may be the first sign of failing hepatic function. A determination of the total serum proteins was done and found to be normal in thirteen cases. However, reversal in the albumin-globulin ratio was found in seven of the thirteen cases; a definite decrease in the albumin content was noted in all of these cases.

The Takata-Ara test was positive in three of the four cases in which it was done. Its significance has not been fully determined and little importance can be attached to this finding at present. A summary of functional tests in a small group of these cases is shown in Table I.

Functional tests as a rule are of more clinical importance in the study of the obstructive types of biliary cirrhosis than they are in the study of other types of biliary cirrhosis. In the obstructive type of biliary cirrhosis much information may be obtained from estimations of serum bilirubin. In the more chronic types of biliary cirrhosis, the values for the serum bilirubin usually vary from 3 to 5 mg. per 100 c.c. In the presence of cholangeitis, values of 8 to 15 mg. per 100 c.c. are common; the higher values usually are indicative of hepatic injury of considerable degree. Retention of dye which is greater than that anticipated as a result of the existing degree of bilirubinemia may occasionally be found. In cases of obstructive types of hepatitis in which there are acute degenerative hepatic lesions, the galactose tolerance and hippuric acid tests may often be positive, and in cases in which the disease is very chronic, some lowering of the value for the proteins in the plasma, and reversal of the albumin-globulin ratio are not uncommon. Macrocytic anemia is common. A summary of the functional findings in a small group of cases is shown in Table II.

To summarize the findings of functional studies in chronic hepatitis, it can be said that the principal disturbances have to do with the excretion of bile pigment, and as a corollary of this, the disturbances of excretion of various dyes. Increasing bilirubinemia indicates a progressive lesion. Other functional tests may be of value in determining the severity of acute degenerative episodes. These tests are of some practical importance, especially in the obstructive types of hepatitis, in estimating the chances for the patient to survive contemplated operation.

PATHOLOGY

Specimens have been obtained from the livers, at operation, in five cases. These are, of course, open to the general objection that they do not necessarily represent a true picture of the general condition of the liver. Furthermore, localized milder changes may be a more or less normal occurrence. In one case in which jaundice had been present for six months, some fatty degeneration, a few collections of lymphocytes between the lobules, and a slight staining of the cells with bile were the only findings. In another case in which symptoms had been present for four years, there were similar changes although they were slightly more prominent. In the other three cases there were similar changes in addition to slight to moderate proliferation of connective tissue. In no case was there evidence of changes in or about the biliary ducts.

Necropsy was performed in nine cases. In one case in which the condition had been present for six months, a subacute yellow atrophy was found. In another case in which symptoms had been present for two years and in which the patient died of an intercurrent infection, a chronic hepatitis was found. This was the only case in which the liver weighed more than normal. In all the other cases there was a chronic atrophy of varying degree. The degree of regeneration varied considerably as did the amount of proliferation of connective tissue; in no case was there evidence of involvement of the biliary ducts. Sections are shown in Figures 1 to 6. It is to be particularly noted that specimens obtained at operation represent early changes, whereas, specimens obtained at necropsy represent a terminal stage of the disease. In other words, the pathologic picture depends on the stage at which the observation is made. These findings, especially notable in the cases of chronic atrophy, are similar to those found in cases in which jaundice is not a significant feature, just as jaundice may be absent in the cases of acute yellow atrophy. It is our impression that jaundice is not a necessary accompaniment of hepatic disease, although its presence is a striking clinical symptom and at once directs attention to the

TABLE II

Hepatic functional tests in various types of obstructive biliary cirrhosis

Patient	Serum bilirubin, mg. per 100 c.c.	Hemoglobin, gm. per 100 c.c.	Macrocytosis	Galactose excretion, gm.	Hippuric acid, gm.	Cholesterol, mg. per 100 c.c.	Cholesterol esters, mg. per 100 c.c.	Serum protein, gm. per 100 c.c.	Albumin-globulin ratio	Takata-Ara test
Bo	13.2	12.3		1.3		225	119	7.0	1:1.24	
Ma	5.3	13.8	+		2.2	345		7.0	1.34:1	
Ti	8.3	9.9		Negative	4.16	735	416	6.55	1.02:1	Positive
Gr	11.1	14.4		Trace	1.72			6.11	1:1.12	Positive
Hwd	8.8	11.4	+		0.41	211	85	6.3	1:1.12	Positive
Mi	7.9	9.6	+	1.03	3.62	416	252	7.1	1:1.3	

liver. Why jaundice is present in some cases and absent in others is at present an enigma.

TREATMENT

Medical treatment of these patients is not very satisfactory. If some etiologic factor, such as chemical poisons, hyperthyroidism, or associated syphilis, can be eliminated, the disease can at times be arrested and recovery takes place. Any definite foci of infection should probably be removed. This perhaps is one important reason for a surgical treatment of associated disease of the gall bladder. Otherwise, therapy is chiefly supportive and symptomatic. The protective value of a high carbohydrate diet is important. The value of insulin in this connection is still debatable. Much relief of pruritus may be obtained from administration of ergotamine tartrate, sodium thiosulphate, or calomel. Anemia can be treated with iron, or with liver extract, as suggested by Goldhamer. Diuretics may aid in eliminating or controlling ascites.

There is considerable weight of surgical authority behind the practice of incriminating the gall bladder and either removing or draining it in cases of chronic jaundice. It must be apparent from the foregoing statement that the procedure has small chance of success except in cases in which there is actual obstruction to the common bile duct or gross infection in the extrahepatic biliary passages. A positive cholecystogram has on more than one occasion been a factor which led to surgical treatment; our own experience leads us to believe that this is probably the last factor which should influence the surgeon. It must be emphasized that cholecystograms in the presence of chronic jaundice or hepatic disease generally should be interpreted most cautiously. Under such conditions the liver is probably unable to eliminate cholecystographic dye at a normal rate and, as a rule, the amounts of the dye which are concentrated in the gall bladder are insufficient to produce a shadow adequate for diagnosis. Even if calculi are demonstrated, their significance is debatable, whether pain has been noted previously or not. In other words, a decision to explore the biliary passages should be based entirely on clinical grounds. Furthermore, cholecystectomy or cholecystostomy in such cases has given indifferent results at best. However, in any case of chronic jaundice, especially if the jaundice is fluctuant or recurrent, the question of exploration must be carefully considered. In many cases it is difficult to determine if a silent stone is present in the common bile duct, and under such circumstances, the risk of operation is entirely justifiable.

A consideration of other surgical procedures may arise in the individual cases. Splenectomy may be considered in the exceptional case, but, as a rule, splenomegaly is purely secondary to the hepatic disease; therefore, the removal of the spleen seldom accomplishes such definite results as it does in hemolytic jaundice or splenic anemia. It may possibly lessen the amount of blood that must pass through the liver and thus reduce the load on the portal circulation. Omentopexy is sometimes considered in cases in which ascites is present. The value of ligation of collateral venous channels which lead to the esophageal plexus perhaps has not been fully explored; it may be a necessary procedure if there is repeated hemorrhage from esophageal varices.

SUMMARY

The term "biliary cirrhosis" implies that the toxic agent enters through the biliary ducts. This is true of the obstructive types of cirrhosis which have been briefly described. The toxic and infectious type and the type associated with chronic atrophy present the following features.

The etiology varies greatly. Hepatotoxins, metabolic intoxication, infections of the biliary tract, and gastro-intestinal tracts, and systemic infections are the cause of the condition in a large number of cases, but there is still a considerable number of cases in which the etiology is unknown. Patients who have this syndrome live for a long time and are resistant both to the disease and to the treatment. There often are entirely unexpected recoveries. In many cases the chief disturbance is in the excretory function of the liver; this is indicated by disturbances in the excretion of bromsulphalein and in the serum bilirubin. The pathologic findings, which vary with the stage of the disease at which the observations are made, do not differ significantly from those found in cases in which jaundice is absent. Finally, it is probably just as unwise to attempt an anatomic diagnosis and establish a prognosis on the basis of a single examination in such cases as it is to do so in a case in which there are signs of parenchymatous renal disease.

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DISCUSSION

DR. ALBERT F. R. ANDRESEN (Brooklyn, New York): As I look at this and the previous paper, they have given us a clinical demonstration of the ability of the liver to regenerate itself, and also of the fact that this regenerated tissue can eventually take over the function of the liver, facts that have been demonstrated experi-

mentally in animals. In our acute cases what we attempt to do is to tide over the patient until the regenerated tissue can take over liver function in its entirety. In the chronic cases apparently the regeneration has kept step with, or has kept perhaps a step ahead of the destructive processes going on, accounting for the patient surviving so long.

Emphasis has been placed on the importance of a high carbohydrate diet and of intravenous glucose administration. I think not enough emphasis is being placed on the observations of Mann and Bollman that in hepatectomized animals the factor causing the most rapid destruction of the individual, the factor that apparently is responsible for the very rapid development of edema and ascites, is the ingestion of meat or meat extracts. This is equally true in the human. In the dietetic treatment of patients with destructive conditions of the liver, avoidance of animal protein (meat) and animal protein extracts, such as broth or soups, is fully as important as the pushing of carbohydrates and calcium.

DR. DAVID REISMAN (Philadelphia, Pa.): The right upper quadrant of the abdomen, which I have called the "Balkans of the body," presents us with more perplexing problems than any other anatomic region. And of all the problems that of chronic jaundice is the most tantalizing. Doctors Weir and Snell in their exhaustive paper show how complicated it is and from the large experience of the Mayo Clinic shed new light upon it. I am not sure but that the title of their essay might profitably be reversed, that is, instead of saying chronic hepatitis with jaundice, to say, chronic jaundice with hepatitis and other non-obstructive lesions. They would restrict the term biliary cirrhosis to that form of cirrhosis in which the toxic agent enters through the bile ducts. I wonder whether such a restriction is not a little too narrow. Is it not more likely that in the toxic cases the poison reaches the liver through the blood? In the so-called Hanot's cirrhosis, a condition which may not be a true clinical entity but in a sense is a type of biliary cirrhosis, the agent whatever it may be must reach the liver as it does the spleen by the hematogenous route. Perhaps the term biliary cirrhosis ought to be applied to that form of cirrhosis in which jaundice is an early and prominent feature and ascites, if it occurs at all, a late phenomenon. True biliary cirrhosis is rare in cases of common duct obstruction by stone. It is, I think, the general experience that mechanical biliary obstruction seldom causes cirrhosis of any kind. Rolleston has pointed out how rarely malignant disease of the pancreas with complete obstruction is associated with cirrhosis of the liver. Stricture of the common duct sometimes is attended by cirrhosis but the cause is probably some form of infection rather than bile retention *per se*.

Considering the frequency of gall stones and of cholecystitis, it is surprising how rarely the liver is the seat of any kind of serious injury. It is in cases with active infection, cholangitis and suppuration in the gall bladder, in which injury of the liver most frequently occurs. Dr. Reuben Ottenberg of the Mt. Sinai Hospital in New York was good enough to look over the records of that busy hospital. In 300 cases of liver disease, there were 10 that were recorded as biliary cirrhosis, in 6 of which the diagnosis was confirmed by operation or autopsy while in 4 it was purely a clinical opinion.

Because the liver is so tolerant—it must have enormous factors of safety since three-fourths of it can be cut away in an animal and the remainder will suffice for all purposes. I am not altogether in accord with the opinion of some of my surgical friends that the presence of gall stones is always and invariably an indication for operation. Dr. Chester Jones in his paper this morning also showed the high degree of liver tolerance that exists.

Doctors Weir and Snell have referred to the distress caused by itching. I believe generalized itching is almost the greatest physical suffering to which the human body can be put. Angina pectoris and coronary pains are intolerable but they pass either in life or death but itching may go on forever. For that reason I favor cholecystenterostomy even if the cause of the jaundice is irremovable, provided it is obstructive.

A number of years ago I wrote a little article on what I called "preicteric itching"—itching present in persons who a few days or weeks later developed jaundice. I have seen similar cases since that publication, which was made before we knew about the van den Bergh test. Perhaps there was a latent jaundice present. It is possible, however, that the itching in jaundice is not due to the bile pigments but to the bile acids or some other constituent of the bile. A fact that might seem to corroborate this idea is the frequent disappearance of the itching within twenty-four hours after the cholecystenterostomy long before there is any visible diminution in the icterus.

I am glad that Doctors Weir and Snell are focussing our attention on jaundice—perhaps their present and future studies will help us better to understand and to treat that important symptom.

DR. CHESTER JONES (Boston, Massachusetts): I am interested in the group that Drs. Weir and Snell have reported. A few years ago I collected 30 patients like this that I had been following for 10 years. I have continued to follow that group and now have several that have been jaundiced for between 15 and 18 years. I shall agree with Dr. Weir that the length of life that some of these patients will carry out is really quite surprising.

The important symptom that most of them complain of, I think, is weakness. Even if they live they are unable to do a full day's work in most instances. I think pathologically they fall into two groups. It may be of some importance to stress those two groups. The two extremes are an atrophic type of cirrhosis, based on original acute yellow atrophy, in which there is complete destruction of the normal architecture of the liver and a rather haphazard of hepatic tissue.

The group at the other extreme is one in which there is a true hypertrophic cirrhosis of the liver. It may be caused by obstruction of long standing or it may be due to infection. In these cases instead of there being a disturbance of the normal architecture of the liver there is a large connective tissue increase between the portal spaces as well as lymphocytic infiltration. In between these two extremes we get almost any variation that we may desire.

In the first group it is important to point out that catarrhal jaundice may be, and frequently is, a cause of the condition which may run on for years. There was an excellent review of cases brought out two or three years ago following an epidemic of catarrhal jaundice in Stockholm. If I remember correctly, prior to that epidemic there had been two or three cases of acute yellow atrophy annually reported to the medical examiner. Following this epidemic, there were 60 cases reported in one year. The pathologic findings in the autopsied cases were all those of acute or subacute yellow atrophy.

One of the cases I followed until two months ago had been jaundiced for 15 years. He and his brother became jaundiced in an epidemic of catarrhal jaundice. His brother lived three months, and this patient lived 15 years. He went through the entire gamut of hepatic failure, prolonged jaundice followed by the development of ascites, which subsequently disappeared. He carried on a fairly active life for almost six years after the ascites was first noted.

The long period of survival is possible if they are well treated in the beginning stages of liver insufficiency. But, weakness and a persistent anemia that does not respond to treatment are two of the outstanding features.

DR. JAMES F. WEIR (closing the discussion): I wish to thank the gentlemen who have so kindly discussed this paper.

Dr. Riesman mentioned the severity of the pruritus that many of these cases have presented. Some of the chronic cases of jaundice without obstruction have presented pruritus as a particularly prominent feature, and almost anything one can do has not been of benefit. In the early days some of these patients with nonobstructive jaundice were subjected to cholecystogastrostomy without any change in the symptoms, particularly the pruritus.

In this group of cases we can emphasize first, that there are some that are related to gastro-intestinal infections; second, that biliary tract infection probably plays a minor rôle; third, that functional tests are not of much value except in the terminal states; and fourth, that most of the unknown types, as far as etiology are concerned, are forms of chronic atrophy.

Macrocytic Anemia in Diseases of the Liver: General Considerations*

By

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THE impetus given to the study of the anemias, initiated particularly by the experiments of Whipple and Robscheit-Robbins and by the contributions of Minot and his collaborators, has served to focus attention upon the group simulating Addisonian, "pernicious anemia," and characterized by the presence of a macrocytosis. From the specific effect of liver in the treatment of pernicious anemia, it seemed evident that more careful studies of the morphology of the blood in hepatic disease were indicated.

Notwithstanding the early observations of Gram (1883) (1), Limbeck (1896) (2), Capps (1903) (3), Talley (1908) (4), Perrin (1908) (5) and those of later contributors, until recently, a macrocytic anemia associated with various forms of liver disease without hemorrhage, (cirrhosis, "catarrhal jaundice," obstructive jaundice, carcinoma) had been regarded as no less than unique. Yet from a review of the literature, more than 200 such cases have been recorded to date, and, unquestionably, many others have been observed but not reported.

In this presentation, it will be shown that a macrocytic anemia, or macrocytosis alone, is a common finding in advanced or widespread liver disease. Its characteristics and therapeutic responses will be reviewed and discussed, and its prognostic significance indicated.

AUTHOR'S STUDY

Complete blood counts including cell volume determinations were performed upon 66 selected patients, in whom the diagnosis of liver disease seemed beyond question. Of these, 42 were diagnosed hypertrophic portal cirrhosis, 4 atrophic portal cirrhosis, 3 hypertrophic biliary cirrhosis, 1 acute yellow atrophy, 10 toxic hepatitis, 3 carcinoma of the head of the pancreas and 3 diffuse metastatic carcinoma of the liver. Parenchymatous jaundice was present in 45 patients, the icterus index ranging between 18 and 187, and averaging 58. In 22 of the patients with jaundice, and in 9 others (cirrhoses), ascites were easily demonstrable. There was considerable variation in the duration of symptoms, being from 1 week, in the acute cases, to 16 years in the cirrhoses; the average for the entire series was 1.3 years. It is apparent from these data that this group as a whole represents advanced or widespread hepatic disease.

The detailed data and observations pertaining to 62 of these patients have been recorded elsewhere (6).

Incidence: Most of the reports that have appeared in the literature have been confined to single case studies or to observations upon small groups of patients. Hence it has been difficult to formulate a true appreciation of its incidence. Meulengracht (17) observed a macrocytosis in all cases of catarrhal jaundice, cirrhosis or hepatic tumor, when they were associated with intense icterus. Similarly, Schulten and Malamos (7) concluded from their studies, that in diffuse liver disease, especially with jaundice, macrocytosis is an almost constant finding. In a review of 100 cases of portal cirrhosis, King (8) alludes to no instance of macrocytic or hyperchromic anemia amongst 57 cases without hemorrhage. On the other hand, Fellinger and Klima (9) found a hyperchromic anemia in 18 out of 48 patients who had various grades of cirrhosis, and expressed the belief that practically all such cases would ultimately manifest this form of anemia. Cheney (10) reported an increased cell diameter in 36.8% of his cases of liver disease, and in 11 out of 12 with hematocrit studies the cell volume was greater than normal. Wintrobe (11) found a macrocytic anemia in 25 out of 132 patients (21.9%) with various types of liver disease, the macrocytosis having been observed only in cases of long standing and very widespread liver damage.

In our observations on 66 patients, a macrocytic anemia was noted in 58 instances (88%). Of the remaining 8, a normocytic normochromic anemia was found in 2 patients with hypertrophic and in 1 with atrophic cirrhosis; a microcytic hypochromic anemia occurred in 1 with hypertrophic cirrhosis, a normal blood count in another case of hypertrophic cirrhosis, and a macrocytosis without anemia in one patient with toxic hepatitis and in one with acute yellow atrophy. The degree of macrocytosis varied within wide limits, the mean corpuscular volumes ranging between 95.4

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and 142.5 c.u., and averaging 113.5 c.u.* The red blood cell counts in this series varied from 1.09 to 4.97 million per c.mm., and averaged 3.45 million. It is worth observing that the 4 patients with the most advanced anemias likewise presented the highest degrees of macrocytosis, whereas the patient diagnosed as relatively early hypertrophic cirrhosis exhibited a normal blood picture. From Chart 1, it is seen that a rather

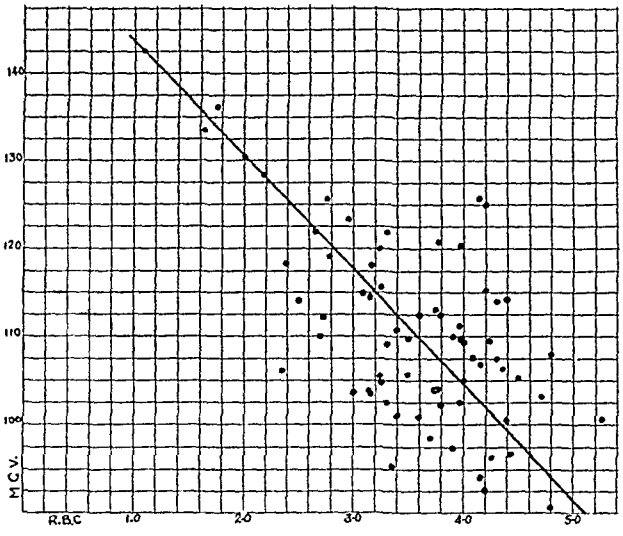


Chart 1. Showing the close parallelism between the degree of macrocytosis and the grade of anemia. As the anemia increases, the macrocytosis becomes more marked. The usual range of the anemia is clearly demonstrated. M.C.V. —mean corpuscular volume in cubic microns. R.B.C.— erythrocytes in millions per cubic millimeter.

close parallelism exists between the grade of anemia and the degree of macrocytosis. However, there was no absolute correlation in different patients between the extent of manifest liver disease and the degree of anemia and macrocytosis, some patients in the terminal stage presenting only a slight macrocytic anemia.

To determine with what frequency actual hyperchromia was encountered in our patients as a group is difficult, for so many presented a bilirubinemia, which, especially when marked, gives a fictitious reading with the Sahli hemometer. But of the patients with little or no jaundice, a hyperchromic anemia was found in 22.

Course: Relatively little has been written concerning the evolution and course of this form of anemia in hepatic disease. Wright (12) found a "tendency" toward the development of a macrocytosis in his 12 cases of cirrhosis. Other observers (9, 14, 15) reported a transition from a microcytic or normocytic anemia to a macrocytic type, concomitant with advancing liver destruction. In a study of experimental cirrhosis in rats, Higgins and Stasney (16) were able to observe the progressive development of a macrocytic anemia, the macrocytosis and the anemia increasing proportionately with the increase in the degree of cirrhosis. Further, Gram (1), Meulengracht (17), Stewart (18), Wintrobe and Shumacker (19) and others observed spontaneous remissions in patients improving or recovering from acute or chronic liver disease, and more recently, Wintrobe (11) noted remissions in 72% of his cases. Similar changes have been encountered amongst several of our patients, and are graphically represented in Chart 2. Of our cases of acute hepatic disease, a macrocytosis was present in one patient as early as the seventh day of illness; in another, it had disappeared within 2 weeks after improvement set in (6). In chronic liver disease the return to normal may take place rapidly or slowly, and may be only temporary, a relapse ensuing shortly thereafter. In none of our patients did the normal mean corpuscular volume become reëstablished. From the foregoing data, it is but a short step to propose that either an increasing macrocytosis or a progressive anemia, in the absence of hemorrhage, may be a useful prognostic criterion in the course of chronic liver disease.

Pathologic alterations have been observed in the blood forming organs of such patients. Bleichroeder (20) called attention to the red hyperplastic marrow in the long bones, particularly the femur, of many of his cases of cirrhosis, a finding which has been corroborated since then by others (9, 21, 22, 23, 11, 24). Isaacs (25) found an appreciable increase in the number of megaloblasts in the bone marrow of 6 patients with cirrhosis and macrocytic anemia, and Rossier (24) noted a decrease in the megakaryocytes. More recently, Rich (26) described multiple foci of normoblasts, macroblasts and myeloid leucocytes in the spleen of some patients with liver disease. It is of interest, therefore, that clinical evidence of active erythropoiesis, as indicated by a reticulocytosis, was obtained in the majority of our patients.

Hemosiderosis, particularly of the liver, spleen and bone marrow, has been observed by Bleichroeder, Rossier and others, and in these cases raises the question of the coexistence of cirrhosis with Addisonian anemia.

Diagnosis from Addisonian pernicious anemia: To distinguish clinically between a macrocytic anemia of the Addison-Biermer type and that accompanying atrophic or some cases of hypertrophic cirrhosis, without hemorrhage, may upon occasion challenge the diagnostic acumen of even the most astute physician. Zeigler (27), Roth (28) and Remen (29) have reported isolated cases in which a clinical diagnosis of Addisonian anemia was made without equivocation, but which at necropsy were shown to be atrophic cirrhosis.

Appearing in middle or late adult life, the semeiology may be identical, dyspeptic symptoms such as anorexia, nausea, vomiting, pain or irregular intestinal motions being present in both diseases. Glossitis and neurologic manifestations may develop in cirrhosis, although they are exceptional, the condition having been observed in but 3 of our series and only subsequent to protracted alcoholic debaucheries. The faintly icteric pallor and the excessive urobilinuria, so characteristic of pernicious anemia, are common findings in cirrhosis. Splenomegaly of a slight or moderate degree is not distinctive for either. But achlorhydria, almost invariably present in pernicious anemia, is far less frequent in cirrhosis, such having been found in 11 out of our 38 cases of cirrhosis which were tested with histidin (6). Although slight or moderate ascites may occur in pernicious anemia, it is found only with the extreme grades of anemia; other signs of portal obstruction are distinctly lacking.

Contrary to Addisonian anemia, in the majority of cases of liver disease, the anemia when recognized is of a slight or moderate grade; hence asthenia is a less

*Normal—80-94 c.u.

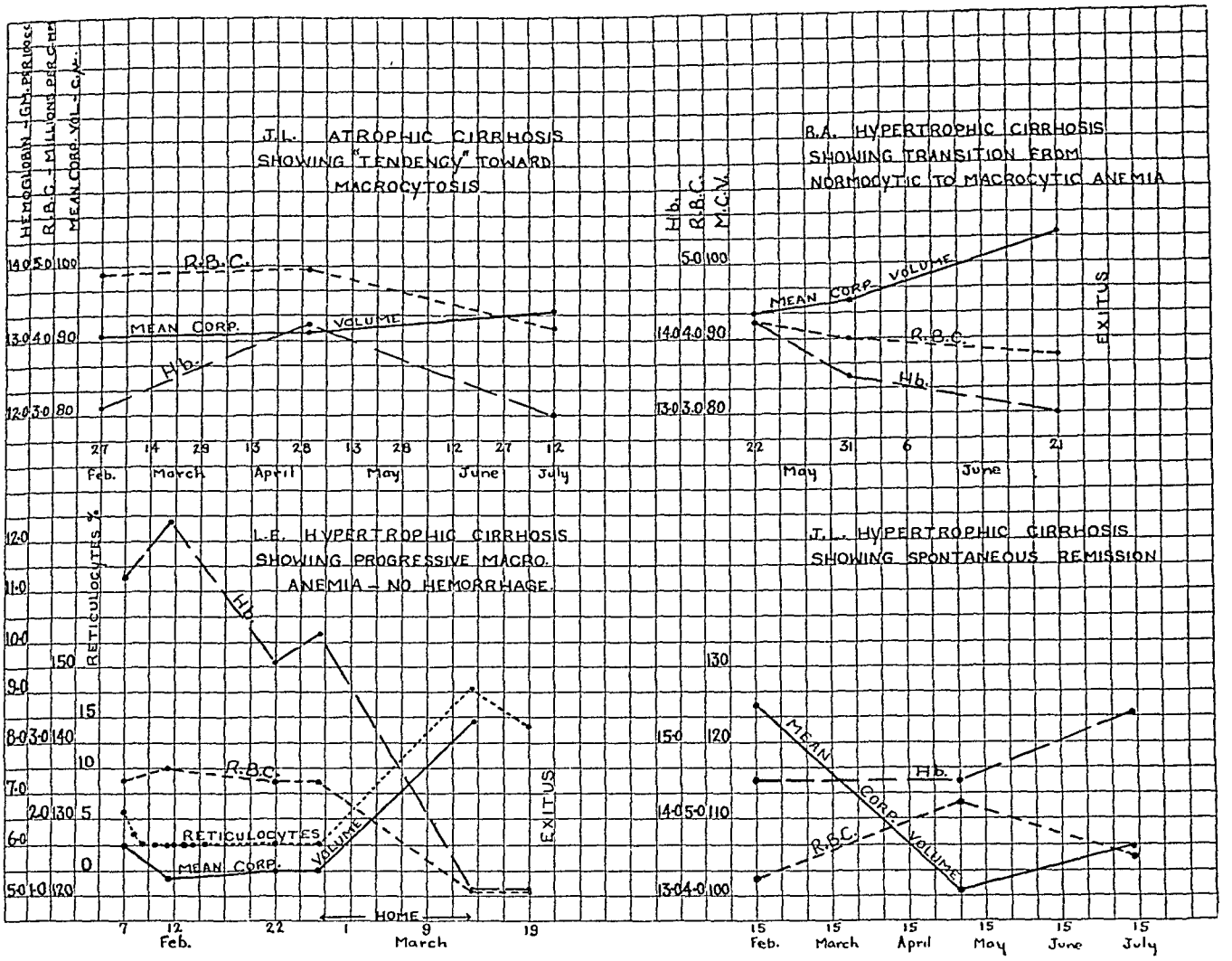


Chart 2. *Illustrating the evolution and course of the macrocytic anemia in liver disease.*

striking symptom. Blood films reveal a slight increase in the diameter of the erythrocytes, the size and shape of the cells being relatively uniform. Price-Jones frequency curves simulate those of equivalent degrees of pernicious anemia (19). In the more advanced anemias, a conspicuous macrocytosis with slight or moderate anisocytosis are in evidence. Poikilocytes and polychromatophilia are less frequent in liver disease, and microcytes and nucleated red cells are seen only occasionally. In one of our patients, giant platelets were noted, and in a small minority of our cases, a leucopenia with a relative lymphocytosis was found. With such similarities, it is apparent that in the differential diagnosis of Addisonian, "pernicious," anemia, particularly in the less advanced forms, thought must be given to the possibility of hepatic cirrhosis.

Treatment: Various results have been obtained through the administration of liver, parenterally or orally. Perrin (5), who employed liver extensively in the anemias of liver disease, noted distinct hematologic improvement, and in some cases, even a polyglobulia. From the reports of 13 cases treated with parenteral "primary anemia" liver extract (13, 30, 19, 11), definite remissions were produced in 8. Yet other investigators (9, 31, 10) consistently noted little or no response.

Of our 7 patients whose erythrocytes ranged from 1.85 to 3.14 million per c.mm. (average 2.38 million) and who were treated with potent liver extract, a reticulocyte rise occurred in 4, being only slight in 3 of these. A moderate increase in red blood cells was noted in 1; in 3 others a slight but significant rise appeared, ultimately returning to the initial level in one despite continued therapy; in the remaining 3, no response was noted. In one patient the blood picture seemed to be maintained at a constant level, for after discontinuing liver therapy, the erythrocytes and hemoglobin dropped rapidly. In none were the hemoglobin values affected.

In explanation of the variability in response to liver therapy, it has been suggested that the liver may play an important *rôle* in the intermediary metabolism of liver extract, little or no effect being evoked in cases with extensive liver disease. Or, perhaps in some, doses larger than those customarily exhibited might have been more uniformly effective.

Cheney (10) observed striking improvement with "secondary anemia" liver extract plus iron, but this did not obtain in Wintrobe's (11) case. In only

1 out of 3 patients (11) was vitamin B therapy efficacious, whereas stomach extract proved valueless in 2 instances (13, 19).

Pathogenesis: The origin of this anemia in liver disease has called forth interesting speculation and thought. Naegeli (32) hypothecated an endogenous toxin as its cause, but no evidence has been adduced in its favor. Meulengracht (17) contended that the macrocytosis was due to a swelling of the erythrocytes, resulting from physico-chemical changes in the blood. Finding a direct relationship between cell size and the degree of icterus, he suspected the bile salts as the provocative agents, but our own failure to observe such a correlation tends to negate this possibility.

More recently it has been pointed out that the common factor in the development of a macrocytic anemia is a deficiency (33, 34) of the hematopoietic principle, either through its defective formation, absorption or utilization. Ivy, Richter and Kim (35) have demonstrated that the active substance is stored in the liver, and Goldhamer, Isaacs and Sturgis (30a) have shown that it is either reduced or absent in hepatic cirrhosis with macrocytic anemia. These observations in conjunction with the experimental results of Higgins and Stasney seem to indicate that the view of a deficient storage of the hematopoietic principle by a diseased liver is the most tenable explanation of today.

However, some of our observations (6) suggest that the explanation may be more complex than that presented above, and that the development of a macrocytic hyperchromic anemia may proceed in at least two stages, either simultaneously or consecutively: *first*, a swelling of the erythrocytes may occur, possibly as a result of a lowered colloid osmotic pressure secondary to a decrease in serum albumin, the latter commonly found (36) in advanced liver disease; and *second*, when the store of hematopoietic principle in the liver becomes sufficiently depleted, true macrocytes rich in hemoglobin appear in the peripheral blood. Careful follow-up studies of the blood, especially in cases of less advanced chronic liver disease, may reveal significant data and may aid in the elucidation of these changes.

SUMMARY

The incidence, course, prognostic significance, pathologic findings, treatment and pathogenesis of the macrocytic anemia occurring in advanced or widespread liver disease are discussed. The similarities and dissimilarities to Addisonian pernicious anemia are reviewed. Attention is drawn to the importance of considering chronic liver disease, cirrhosis in particular, in the differential diagnosis of mild and moderate grades of Addisonian "pernicious" anemia.

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DISCUSSION

DR. M. M. WINTROBE (Baltimore, Maryland): Dr. Rosenberg has presented a very able summary of the literature and has made some very interesting observations of his own.

He has emphasized the fact that in many instances the differentiation of pernicious anemia and the macrocytic anemia of liver disease may be difficult. I should like to stress, however, that this is the unusual rather than the usual course of events. In most of these cases the picture of liver disease is a very clear and definite one. In fact, I think the failure to recognize until recently that macrocytic anemia occurs in some cases of liver disease is largely due to the fact that the picture of liver disease is usually so prominent that complete studies of blood often are not made. These patients may show variable degrees of jaundice or ascites, large livers and impairment of liver function.

I am rather surprised at the very high incidence of macrocytosis in Dr. Rosenberg's cases.

(Slide) We have made a clinical and pathological study of 132 cases of liver disease of all kinds, and 34 of these were studied after death, the tissues being examined microscopically in these cases. We found that macrocytic anemia was present in 43 of the 132 cases. However, I think that some of these cases should be excluded from the series for various reasons.

First of all, some of these were instances of hemolytic anemia, which in itself might cause macrocytosis. These cases very probably do not belong in the group under discussion.

Furthermore, in a number of cases the mean corpuscular volume was only slightly in excess of normal and in some instances was only determined once.

I should like to emphasize that although the determination of mean corpuscular volume is of considerable value it is also open to a good deal of error and one ought to be very cautious in the interpretation of the results unless they are confirmed repeatedly. Incomplete packing of the red cells, or a slight difference in the red cell count may give misleading results. In my own experience errors tend to give a macrocytosis rather than the opposite.

For these various reasons we excluded 18 of our cases. This leaves very definite macrocytosis in only 25 cases, or 22 per cent.

I should like to ask Dr. Rosenberg whether pathological studies were made of the livers of his cases to determine the correlation of the nature of the liver damage with the type of anemia found.

This is a point which I would like to emphasize, namely, the relation of the type of liver disease to macrocytosis. From these figures you will see that it was in the cases of cirrhosis that the incidence of macrocytosis was high. In the cases of malignancy with cirrhosis, macrocytic anemia

was very frequently found. This type of anemia seems to occur in cases of liver disease in which the liver disorder has been of long duration and is extremely widespread, a finding which rather tends to support the hypothesis that the anemia may be the result of faulty storage or formation of anti-anemic principle.

In observations which we are going to report this afternoon at the meeting of the American Society for Clinical Investigation, experiments were carried out in dogs and in rabbits which tended to corroborate these findings, namely, that the macrocytosis appeared only in those instances in which the liver damage was of long duration and extremely wide spread.

DR. DAVID H. ROSENBERG (Chicago, Illinois, closing the discussion): I think it is worthy of emphasis that the type of patients which we selected for study did represent, we felt, advanced and widespread liver disease, as shown by the data presented at the beginning of the paper.

Furthermore, Cheney, of California, in studying the cell volume in 12 cases of liver disease, found 11 of these patients with an abnormally high cell volume, whereas when actual cell diametric measurements were made, macrocytosis was found to be present in 37 per cent of all of his cases.

Post mortem studies were available in nine patients and of these, one was a case of acute yellow atrophy and the other eight, cirrhosis. All of them showed extensive and widespread disease of the liver.

Concerning the relationship of the nature of liver disease to the development of macrocytosis, I agree that the macrocytosis occurs only when one finds advanced or widespread liver disease.

Anemia and the Gastro-Intestinal Tract*†

A Synopsis

By

GEORGE R. MINOT, A.B., M.D., S.D., F.R.C.P. (Edin.)

BOSTON, MASSACHUSETTS

NUMEROUS concepts of an association of anemia and the gastro-intestinal tract and its contents have been expressed in various ways for more than a century. It is, however, only during recent years that it has been clearly recognized that anemia often is dependent on defective nutrition, and that derangements of the gastro-intestinal function can be responsible for impoverishment of blood formation. So far as the digestive tract itself is concerned, the focus of attention has been directed to the stomach. Even as long ago as 1855, the year that Addison's second, but best known, description of "idiopathic anemia" (pernicious anemia) was published, C. Handfield Jones (1), who studied the stomach histologically, wrote after describing the case of a "very anemic" man, 62 years old, with "marked atrophy of the glandular tubes" [of the stomach], "Here is a case of extreme wasting of the secretory structure of the stomach coinciding with like wasting of the blood without any apparent cause." He also mentions "That inflammation may and often does produce atrophic changes is perfectly true, but I can not but regard it as a mischievous error to assume that it is the only or the most frequent cause of such changes." Further on he writes, "These morbid changes I believe to be coincident results of depraved nutrition . . . ." The last remarks are of historical interest in relation to today's knowledge that gastric atrophy and achlorhydria may develop with dietary deficiency.

A prophetic statement was made by Austin Flint (2) in 1860 when he wrote, "Nor is it difficult to see how fatal anemia must follow an amount of degenerative disease reducing the amount of gastric juice so far that the assimilation of food is rendered wholly inadequate to the wants of the body."

Samuel Fenwick's (3) studies represent the significant pioneer work in this field. In 1870, he described a typical case of pernicious anemia with great atrophy of the "secreting tubules (of the stomach) converted into a mass of connective tissue." He showed that pepsin was absent. He wrote, "The progressive atrophy of the stomach had prevented the digestion of the albuminous materials of the food." Fenwick apparently considered that this was the cause of the anemia and wrote that "Perhaps future investigators may prove that the anemia [in another type of case] arises from a coexisting atrophy . . . of the stomach or other parts of the digestive canal." In subsequent papers and in his book published ten years later, he records further distinctive observations and remarks concerning the relation of the blood to the state of the digestive tract. Many studies concerning the stomach in pernicious anemia followed by such men as Cahn and von Mering, Kinnicutt, Quinsel, Faber and Block, and Hurst. There are also many early references, mostly rather vague in nature, to the relationship between the gastro-intestinal tract and hypochromic anemias, especially chlorosis. There was a waxing and waning interest in this subject in general until 1928 when Castle, after subjecting to experiment his brilliant original ideas, proved with his collaborators the important *rôle* of a factor secreted by the normal stomach which is essential for normal blood formation.

(Following this introduction there was reviewed with a series of 30 lantern slides, first, problems concerning macrocytic anemias due to deficiency of material effective in pernicious anemia, and then various aspects of hypo-

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†The Abbott Lecture: Established by Frank Smithies, M.D., Chicago, 1929, but now maintained by the Association.

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chromic anemia due mainly to iron deficiency. A synopsis of the lecture is given below):

THE MACROCYTIC ANEMIAS OF NUTRITIONAL DEFICIENCY

Pernicious anemia and related macrocytic anemias have been shown by Castle to be dependent upon a nutritional disturbance conditioned by the state of the gastro-intestinal tract. The normal individual can derive material from food needed to prevent pernicious anemia by means of gastric digestion. Deficiency of the gastric factor, of the dietary factor, or of the material within the body proper originating from the interaction of these two factors leads to macrocytic anemia. The factors may interact somewhat in accordance with the law of "mass action." Disorder of the intermediate or internal metabolism of "liver extract" may perhaps occur. It is unreasonable to blame faulty storage in the liver alone as a cause of macrocytic anemia for the potent material occurs in other organs, such as the kidney and brain.

The varying and atypical results produced by the parenteral injection of gastric juice await elucidation. The observations must be evaluated with the recognition that there are many unrelated substances that can induce non-specific reticulocyte responses.

Greenspon (4) has recently claimed that the gastric factor is a hormone effective directly on blood production. He asserts that in Castle's experiments pepsin destroyed the gastric factor when gastric juice was administered alone, and that beef muscle and certain other foods act simply to adsorb pepsin rather than that they contain a dietary factor. There are various reasons for considering that Greenspon's contentions are unlikely. For example, (*1*). Helmer, Fouts and Zerfas (5) have shown that depepsinized and neutralized gastric juice is inert and that its incubation with small amounts of "fraction G" liver extract of Cohn increases this material's potency several times. (*2*). Responses have been shown (6) to occur when gastric juice and suitable food are fed over six hours apart. Thus, the interpretation of a positive response to gastric juice alone is invalid when food is given four hours after gastric juice, as took place in a crucial experiment Greenspon performed.

Residual amounts of intrinsic factor are present in most cases of pernicious anemia so that a continuously progressive decrease of the blood to the vanishing point does not occur. It takes less liver extract to maintain one million than five million red blood cells. A slight increase of intrinsic factor with a good diet can permit a higher blood level, but it takes much more to maintain an entirely normal blood picture.

To believe that polycythemia is due to excess of liver extract or gastric factor necessitates the assumption that polycythemia can be induced in any normal individual by administration of liver extract or of stomach tissue. This can not be done. The red cells may rise temporarily above normal in recovery from macrocytic or hypochromic anemia simply because the volume of the marrow subsides more slowly than delivery of its contents.

Meulengracht has shown the relatively high potency of the pyloric and cardic portions of the stomach and of the duodenum for the gastric factor. The gastric factor is perhaps secreted by aberrant gastric tissue as in Meckel's diverticulum (Morrison (7)). Gastrectomy leads rarely to macrocytic anemia; very frequently to hypochromic anemia. The secretion of the gastric factor by the duodenum may explain the former state of affairs. The latter condition is associated with defective iron absorption which is discussed further on. The rapid intestinal emptying and modified diets that occur in such instances play a *rôle*. The store of liver extract in the normal body can be estimated as sufficient to prevent pernicious anemia for one or more years.

The repair with therapy of lesions in the stomach is comparable with those of the tongue, as shown by Chester M. Jones. Previous observers studied the gastric mucosa in relapse. Jones has shown the change "from the appearance of atrophy to that of normal gastric mucosa" following liver therapy; an epithelial change due to replacement of a specific deficiency rather than the healing of an inflammatory lesion. In spite of this, achlorhydria almost always persists and apparently the intrinsic factor rarely increases more than slightly.

The conditions causing failure of gastric secretion must be sought. Gastritis, as Faber and Hurst believe, may be important. An hereditary susceptibility may exist. Defective diets can produce widespread changes in the alimentary tract. Miller and Rhoads have produced achlorhydria, lack of intrinsic factor, and macrocytic anemia in pigs by diets defective in vitamin B_2 or a closely related substance. Thus, a non-infective condition can create the defect seen in pernicious anemia. Bad diets can lead to achlorhydria in man. Certain alterations in various hormone actions also can lead to achlorhydria. The effect of anemia, *per se*, on gastric function should not be lost sight of. Dietary deficiency certainly intensifies the picture of faulty gastric function. The applicability of Miller and Rhoads' studies to the etiology of cases of macrocytic anemia arising in the tropics and shown to be due to defective diet can scarcely be doubted, but how far dietary deficiency is operative directly in all cases of macrocytic anemia awaits further study.

Defects of absorption may contribute to deficiency of active products in anemia as in other deficiency states. There is a lamentable lack of knowledge of alimentation. There are innumerable factors that have to do with absorption. The fact that *usual* doses of liver extract given intramuscularly are sometimes maximally effective when treatment by mouth fails suggests that material is not adequately absorbed. This is even more likely because of the association of pernicious anemia with intestinal stenosis and short circuits of the intestine, and its origin with protracted diarrhea as in bacillary dysentery. Occasionally, a patient with an intestinal short circuit, maintained with difficulty on liver extract administered orally, is able to maintain his blood without taking liver extract after the intestines have been returned to essentially their normal state by operative procedure. This is further evidence of faulty absorption. In many instances probably the state of nutritional deficiency leads to gastro-intestinal defects hindering absorption and thus intensifying the disease process.

Tests for defective absorption are needed. The absorption of iodine is often delayed in deficiency conditions and becomes more rapid as a deficiency is met. The delay is perhaps a rough measure of disturbance of the absorptive ability of the upper small intestine (8). The degree of eosinophilia developed from the feeding of raw liver can not at present be definitely related to intestinal permeability. Studies by intestinal

intubation may be shown to be of value. X-ray observations can indicate changes of tone, and activity which may adversely affect absorption of dietary factors.

In diagnosis it must not be forgotten that frequently gastro-intestinal symptoms occur for years before anemia is obvious and that gall bladder disease is common in pernicious anemia.

Tongue, aesophageal, gastric, and intestinal lesions may appear in the macrocytic anemias of nutritional deficiency when the blood is normal or essentially so. Their occurrence is dependent upon activity of the intrinsic factor. In sprue, such lesions are more prominent and extensive than in pernicious anemia and often occur without macrocytic anemia. Liver therapy, however, heals the lesions and their presence demands enough potent material to banish them, disregarding the state of the blood. Indeed, the effect of liver and stomach treatment on the gastro-intestinal tract in *early cases of pernicious anemia, sprue, and certain* atypical cases with gastro-intestinal symptomatology is striking.

Iron deficiency anemia may develop in sprue and during liver therapy in pernicious anemia when iron will alleviate the anemia, but liver must be given to affect the gastro-intestinal symptoms or for maintenance of health.

HYPOCHROMIC ANEMIA

Hemoglobin deficiency is the feature and may arise from lack of material other than iron needed to build the hemoglobin molecule. There are many other factors than iron that can influence hemoglobin production. Iron, however, can cure many cases of hypochromic anemia and it has been shown in man (Heath, *et al*) and dogs (Whipple, *et al*) (9, 10) that, following injection, iron will be returned quantitatively as new formed hemoglobin. In large part the metabolic need in these cases is satisfied by iron. When this need is met the blood-forming organs can respond to the real stimulus which is the anemia. There has been much discussion regarding the most effective type of iron (11). In dogs, Whipple has shown the determining factor is the metal iron, and such seems to be the case in man when iron is given parenterally. In human disease, it appears that ferrous salts are often more effective by mouth than ferric salts, as Ashwell suspected in 1836; and that disorder in the intestinal tract may increase the difference between the effectiveness of the two types. It remains, however, a fact, as mentioned by Osler in 1885, that the important thing is to administer enough of a given kind of iron rather than to debate on what is the smallest dose of iron in some particular form that gives maximal effects.

Names have tended to obscure the close etiological relationship of the various varieties of hypochromic anemia associated with iron deficiency. The basic mechanisms for the origin of this type of anemia are an inadequate intake for the needs of the given organism, faulty absorption or utilization of iron, and loss of this element from bleeding or from transfer to a foetus. As in other deficiency states in anemia, infection, severe damage to organs, and the like may inhibit nutrition and hinder the action of such therapeutic agents as liver extract and iron. In any given case usually several factors are operative and occasionally there occurs in the same individual a deficiency of both iron and the principle effective in pernicious anemia. Rarely one individual may pass through life and be said to have had each one of the varieties of hypochromic anemia mentioned below, which simply implies that throughout life she had an inadequate supply of iron and material for hemoglobin manufacture for her given needs.

The answer to why hypochromic anemia is much more common in women is to be found largely in the fact that under ideal circumstances woman requires for health about four times as much iron as man, up to the age of the menopause.

The nutritional anemia of infants, especially prevalent in artificially fed babies, is dependent on insufficient storage and intake of iron to meet the demands of growth.

Chlorosis, as Stockman noted in 1895, develops at an age when the need for iron rapidly increases due to growth and menstruation; the latter must be offset by the intake of 1 mgm. of iron a day per year. If one adds the growth requirement for the age fourteen to fifteen to the loss from menstruation there is about a 1000 cubic centimeter drain of blood on the iron store. Add to this a poor diet, infections, altered digestion and absorption, and recognize the vicious circle that arises with the development of anemia; then the reasons for iron deficiency of the type called chlorosis seem evident. Heath and Patek (12) have set forth evidence for this point of view. The condition, in part, has disappeared because some cases called chlorosis are now recognized as peptic ulcer, tuberculosis, etc.; and, in part, probably because of the greater frequency of high iron diets. There are many cases of mild anemia today at the chlorosis age; disordered digestion is sometimes given as the cause. It is also not rare to see cases of severe anemia at this age which are apt to be given other names than chlorosis, partly because the causes, such as depraved appetite, slight excess menstruation, etc., are recognized.

The common hypochromic anemia of pregnancy can often be related to the extra demands for iron and to the defects of gastric secretion. It can be prevented by administration of iron.

So-called "idiopathic" hypochromic anemia, very rarely seen in males, can be accounted for particularly by the accumulative effects of the factors mentioned; and with onset of the condition these same causes become aggravated, thus intensifying the deficient state. It is common to find that these women have had gastro-intestinal symptoms for years and present the picture of "chronic intestinal nervous invalids," who have often partaken of diets low in protein and iron for a long time. Altered bile secretion may occur and, among other gastro-intestinal defects, may perhaps hinder the absorption of iron. The flabby atrophic tongue, seldom raw, and achlorhydria with increased mucous secretion are features. The Plummer-Vinson syndrome, originally described by Brown Kelley and D. R. Paterson in 1919, seems to be in these cases dependent on esophageal spasms and webs due to atrophic and associated changes of the epithelium and underlying structures. Indeed, it is alterations of this type that are to be found in very severe cases throughout the intestinal tract, as reported by Schmehle and Schmid (13). These alterations are nutritional, not primarily inflammatory. Full doses of iron totally change the picture; the improvement in gastro-intestinal symptomatology and appearance of the tongue being fully as striking as the improvement in the blood. Achlorhydria is prone

to remain present. It is yet to be proved exactly what factor is responsible for the gastro-intestinal lesions. The better appetite developed and better diet soon taken, once the patient receives enough iron, make it seem possible that numerous dietary factors may play a *rôle*. The symptoms and signs referable particularly to other ectodermal structures, such as the defective nails and atrophy of skin, and the readily bleeding uterine mucosae and ease of skin capillary leakage, are also dramatically affected by iron administration.

In a rare case of *polycythemia* one may find achlorhydria, atrophic tongue, and such gastro-intestinal symptoms as nausea, flatulence, and constipation. In such cases the color index is distinctly low although the red cell count may be well over 6,000,000 per cubic millimeter. These cases probably represent instances of iron deficiency occurring in the face of increased red cell production.

Chronic blood loss by itself is a common cause of hypochromic anemia. Iron therapy is always effective and the liver fraction insoluble in 70 per cent alcohol (not liver extract effective in pernicious anemia) can also enhance hemoglobin regeneration. In diagnosis it may be said that, with proper exceptions, severe hypochromic anemia in a male, which at first appears to be of obscure etiology, will after proper study often be shown to be due to recurrent asymptomatic blood loss from the gastro-intestinal tract.

The relation of the gastro-intestinal tract and its contents to iron deficiency anemia is a significant one. A host of factors bear on this subject. One must distinguish between effects being primary and contributory causes. Disease itself causes motor and secretory dysfunction and thus sets up a vicious cycle. Whatever leads to rapid gastric or small intestine evacuation and loss of tone diminishes the amount of iron taken into the body from the amount available in the diet.

Iron in food is present as ferric iron. The normal availability of food iron is sometimes less than fifty per cent of the iron contained in a given food. Iron is absorbed as ferrous iron. During digestion, the combined effects of low oxygen tension, abundance of readily oxydizable substances, and an acid reaction provide conditions in which conversion of ferric to ferrous iron is made likely to occur. Whatever handicaps diffusion of ferric salts decreases their effectiveness on oral administration. Certain mixtures of food may handicap the absorption of iron. The amount of phosphorus in milk as contrasted with that in orange juice can act to bind appreciable amounts of iron as insoluble salts (14). There are substances such as chlorophyl that appear to potentiate the action of iron. Factors that may enhance and hinder the utilization and absorption of iron require study, while the whole problem of iron metabolism and its interrelations to other factors that influence hemoglobin regeneration is far from solved.

Hypoacidity and anacidity may be considered to play a part directly or to indicate a significant disturbance of absorption capacity of the alimentary tract. Iron is absorbed particularly in the upper small intestine and an acid medium favors the process. If no acid is poured from the stomach into the duodenum the contents will tend to be less acid than normally, and thus iron absorption can be handicapped. The lack of hydrochloric acid and the gastric enzymes can decrease the ease with which iron is liberated from the complexes which contain it in the food. Achlorhydria may be a sign of other defects such as hasty peristalsis, atony, or pathological changes in the gastric mucosae or small intestine which may act unfavorably for iron absorption. Excess of mucus, often present with achlorhydria, can firmly absorb iron and thus perhaps render its absorption difficult.

The action of achlorhydria to antagonize the absorption of iron is also reflected from therapeutic studies in man. It appears that cases of "idiopathic" hypochromic anemia with achlorhydria usually require distinctly larger doses of iron for hemoglobin to regenerate at a maximal rate than cases of hypochromic anemia without achlorhydria, as for example especially those due only to chronic blood loss. Small doses of iron in the former condition frequently have essentially no effect at all while they can cause in the latter type of case distinctive hemoglobin increase but at a submaximal rate.

The types of anemia mentioned—those due to deficiency of material derived from food—will not arise with a healthy intestinal tract, a proper diet for the needs of the given individual at each period of life, and with the absence of abnormal blood loss or factors acting to inhibit nutrition. Much suffering from anemia can be prevented if every person, especially women, takes an optimal diet throughout life. Also, the establishment of early diagnosis followed by proper treatment for each and every aspect of the given individual's case will lead to the prevention of many severe cases of anemia. There is certainly an important interrelation of food, stomach, and intestine in the maintenance, not only of the blood, but also of the integrity of the normal individual.

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Intubation Studies of the Human Small Intestine: VIII. - Miscellaneous Observations*

By

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W. OSLER ABBOTT, M.D.**

and

W. G. KARR, Ph.D.

PHILADELPHIA, PENNSYLVANIA

IN May, 1934, Miller and Abbott (1) described a technique for the rapid introduction, under fasting conditions, of a double-lumened rubber tube into the upper intestinal tract of man and referred to the possibility, by such a method, of studying the secretory and motor functions of the human bowel. Scheltema (1908) (2), Einhorn (1919 and 1921) (3, 4), and Buckstein (1920) (5), had previously accomplished intestinal intubation, but their tubes were of small calibre, required much time for introduction and were designed only for the injection of solutions or suspensions into the bowel. Both Buckstein and Einhorn, however, referred to the possibility of the aspiration of intestinal contents, and, in 1930, Thompson, Einhorn and Coleman (6), using the Einhorn jointed tube, succeeded in aspirating both small and large intestinal contents for a study of the bacterial flora. Jones (7), so far as we know, was the first (1931) to introduce into the lower ileum and colon a tube with an attached balloon, but his apparatus provided no means for the aspiration of intestinal contents.

The chief claims for the original technique developed in our Clinic were that, under strictly fasting conditions, it permitted intubation of the small intestine within 4 to 6 hours and that it at the same time provided a means for exhaustive study of the bowel under essentially normal conditions. These purposes were accomplished by the attachment, at the distal end of the tube, of a balloon which could be distended when the duodenum was reached and which then served as a foreign body that was readily carried along aborally by peristaltic waves. At the same time, by having the tube double-lumened and of adequate calibre, aspirations and injections easily could be made through the lumen that was not connected with the balloon, while the balloon itself could be used to record pressure changes within the bowel.

Since then the apparatus has been modified and the technique perfected (8, 9) so that the entire small intestine usually may be intubated within 3 to 4 hours; so that specimens of the contents may be obtained under conditions of constant but slight negative pressure; so that pressure changes within the bowel may be graphically recorded while the intestinal activity is being observed under the roentgenoscope, and so that a segment of the bowel may be isolated between balloons, its uncontaminated secretion obtained and measured and its absorptive power tested.

It is admitted, however, that the method is not as yet strictly practical for routine use and that it requires considerable experience and much time and patience on the part of the investigator. Some failures inevitably occur, but in over 300 attempts at intubation, mostly on new subjects, Abbott has been successful in 70 to 80%. Often, even on the first attempt in a new subject, the tube reaches the duodenum within 10 minutes, the jejunum within 20 minutes and the lower ileum within 2 to 3 hours.

AUTHORS' STUDIES

At this time we wish to refer very briefly to certain observations that have been made in our Clinic by this technique, some of which have been published, and to point out other lines of clinical investigation that the method seems to render feasible.

Karr and Abbott (10) have already reported on certain chemical studies of the normal intestinal contents under fasting conditions and as influenced by the oral administration of acids, of alkalies and of water. They have confirmed the results of animal investigations, showing that, in the normal under fasting conditions, the reaction of the contents of the duodenum is usually slightly acid, while that of the jejunal and even the ileal contents is slightly acid to neutral, rarely alkaline; that the osmotic pressure of the duodenal contents is usually hypotonic, but that as lower levels are reached approximate isotonicity with the blood plasma is attained.

Miller and Karr (11) have shown that variations in the reaction of the intestinal contents are related not only to variations in the reaction of the stomach contents but also, and perhaps chiefly, to variations in the motility of the contents of the stomach and of the intestine. Thus, in a hyperacidity case (11, Exp. 39) the jejunal contents were approximately neutral until a gelatin solution was orally administered, whereupon, though such a protein solution would tend to neutralize the gastric acid, a distinctly acid reaction of the jejunal contents resulted: this was coincident with an increased rate of flow from the stomach. A similar increase in the acidity of the jejunal contents occurs for a time in normal cases after the administration of water and is coincident with an increased rate of gastric evacuation (10, Fig. 4). In such instances, however, the motility is soon diminished and the reaction of the intestinal contents promptly comes back to approximately neutral. Furthermore, when a highly

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acid solution was administered to an achlorhydric subject (11, Exp. 28) no increase in the acidity of the ileal contents occurred at any time, presumably because evacuation from the stomach was sufficiently slowed to permit neutralization before the contents reached that level.

Thus, apparently it is only for a short time that the stomach, even when its contents are hyperacid, evacuates them rapidly enough to alter the intestinal reaction; then adjustments are made which restore the normal fasting reaction of the intestinal contents. Pylorospasm or duodenal control of gastric emptying is no doubt one of the biologic mechanisms designed to bring about this return to a normal reaction. Such control of gastric evacuation is observed clinically in certain cases of hyperchlorhydria and experimentally after the oral administration of various hypertonic solutions. Probably in achlorhydric subjects with diarrhea the administration of a strong hydrochloric acid solution sometimes has its beneficial effect by calling into action such duodenal control of gastric emptying.

When, on the other hand, the gastric contents of a normal subject are partially neutralized by the administration of a *hypotonic* solution of sodium bicarbonate, a rapid gastric evacuation and a rapid rate of flow through the intestine occur. When, however, the alkaline solution is *hypertonic*, the contents are evacuated slowly (10, Fig. 3). Thus one has an explanation for the laxative effect of a small dose of sodium bicarbonate in some individuals and for the fact that others may habitually take large doses without any stimulating action on the bowels. In like manner, water on an empty stomach may have a laxative effect by reducing the acidity and the tonicity of the stomach contents and so leading temporarily to a rapid rate of flow through the bowel.

These considerations lead one to wonder what occurs in the intestinal tract after the ingestion of ordinary food substances. Do the contents then maintain a neutral reaction and isotonicity with the blood plasma? Let us consider for the moment only the carbohydrate foods. In the first place, most of the natural foods that contain carbohydrate, such as milk, breadstuffs, vegetables and most of the edible fruits, are hypo- or isotonic. When certain fruit juices, high in sugar, or hypertonic solutions of sugar itself are ingested several mechanisms, similar to those for excessively acid or excessively alkaline solutions, seem to be brought into action to prevent entrance of the gastric and duodenal contents into the bowel in such a state. Ravdin and his co-workers (12) have demonstrated in animals that in no matter how concentrated a form glucose is administered to the stomach it becomes isotonic before it passes into the intestine. We (13) have shown the same phenomenon in man, have demonstrated that a further decrease in concentration occurs as the glucose passes through the duodenum and that the percentage concentration is even further reduced as lower levels of the intestine are reached, even to less than one per cent in the ileum. Under such circumstances isotonicity is maintained by variations in the electrolyte content (10).

Having shown, therefore, that ordinarily glucose appears in the intestine in less than 5.4 % concentration (isotonic solution), we next have attempted to determine its rate of absorption, confining most of our investigations to solutions at or below that concentration. Using isolated loops of bowel, into which were introduced 50 c.c. amounts of solutions of varying strength and removing the residue after fifteen minutes, we have demonstrated an increase in the rate of absorption with an increase in the concentration of the glucose solution.

We have only a few observations on the fate of hypertonic solutions of glucose in the intestine. It seems reasonable, however, that after the ingestion on an empty stomach of very sweet foods, such as orange juice, berries, preserved fruits or candy, some early escape into the intestine of sugar at a higher concentration may occur. Our data suggest that the intestine reacts to such a hypertonic material by an outpouring of fluid into the bowel, by increased peristalsis and motility and by the secretion of mucus. These reactions doubtless account for the clinical observation that some persons develop a diarrhea after taking such substances. Such diarrhea may also be dependent in part on changes in the tonus of the intestinal musculature. Some experiments on the intestinal action of morphine by Abbott and Pendergrass (14), using our technique of intubation, have suggested that the effectiveness of a substance upon intestinal motility may depend as much upon its action on muscular tonus as upon the height and frequency of peristaltic waves. This deserves further study, and the combined use of the multiple-lumened tube and roentgenoscopy seems to offer a means for such investigation.

The technique has also presented an opportunity to restudy the reference of pain from various points along the small intestine. Such studies were previously made by Jones (7), utilizing a balloon on a single-lumened tube; but our results, though in a measure confirmatory, show variations that deserve consideration. He was interested chiefly in pain produced by distension of the balloon when in the large intestine, but stated that when the balloon was distended in the jejunum or ileum pain for the most part was referred to the mid-line just above or below the umbilicus respectively; sometimes to the back. Our method has been to distend the balloon, while the subject was under the roentgenoscope, until discomfort was produced: at that time marks were made on the screen to indicate the exact location of the balloon and the point at which the subject with his own finger localized the pain. Reference to Chart 1 will show that the marks were superimposed only once, but that in the majority of instances pain from the jejunum was referred to a point above the umbilical line; from the ileum, to a point below that line. More specifically, when the balloon was in the jejunum the pain was referred to the upper abdomen 7 times, to the umbilical level 3 times and below that level only once; when the balloon was in the ileum the pain was referred to the lower half of the abdomen 11 times, to the umbilical level 5 times and above that level 4 times. When a circle with a radius of 10 cm. was drawn about the umbilicus it showed the point of referred pain from the jejunum to be outside the circle in 6 instances and inside it in 5; that from the ileum, to be outside the circle in 4 instances and inside in 16. Thus, in our subjects referred pain from the ileum was usually located below the umbilical level and within 10 cm. of the umbilicus. The location of the balloon in the abdomen had no relation to the point of referred pain. It is to be appreciated that this work refers only to pain

produced by distension of the bowel wall; the pain and tenderness produced by inflammation may have a different localization.

We have as yet made but a few bacteriological studies on the intestinal contents. In that the technique, however, affords an opportunity to enter the bowel quickly while the subject is fasting or at any desired time in the course of feeding experiments, it would seem to have an advantage over the method employed by Thompson and his coworkers (6). It obviously has many advantages over methods which involve the collection of specimens from fistulae, either in animals or man, in which skin contamination and a disturbed physiology of the bowel must be considered.

Finally, we wish to call attention to certain opportunities in the method for the study of persons with abdominal disease. We have not hesitated to intubate patients with unexplained abdominal pain, with abdominal distention, with ulcerative colitis, Addisonian anemia, common bile duct obstruction, a gastro-enterostomy and even one patient with intestinal obstruction from carcinoma of the cecum. In another patient with small intestinal polyps we were able to introduce a barium mixture into the affected small intestinal loop and so with the aid of the roentgenoscope bring clearly into view the fixed negative shadows. By placing the opening for aspiration at the distal end of the balloon in the patient with obstruction, pus was removed ahead of the balloon and peristaltic waves carried the apparatus into the upper ileum. A special modification of the tube has been designed by Abbott (15) for insertion into the stomach through the nose preoperatively and then at operation for the passage of its distal part through a gastro-enterostomy stoma; thus it permits subsequently the aspiration of stomach contents through one lumen and the administration of fluids directly into the jejunum through the other, and so obviates the necessity of post-operative intravenous injections. In one instance, in a very seriously ill patient, this modified tube was inserted at operation through a gastrostomy and then through a gastro-enterostomy stoma: it functioned satisfactorily for ten days and at autopsy no evidence of irritation about the stoma was demonstrable.

Thus, briefly, we have outlined certain investigations and therapeutic procedures carried out by our method of intubation and have indicated some further uses for the technique, in which, however, our experience is as yet limited. We hope the technique may prove useful to other investigators.

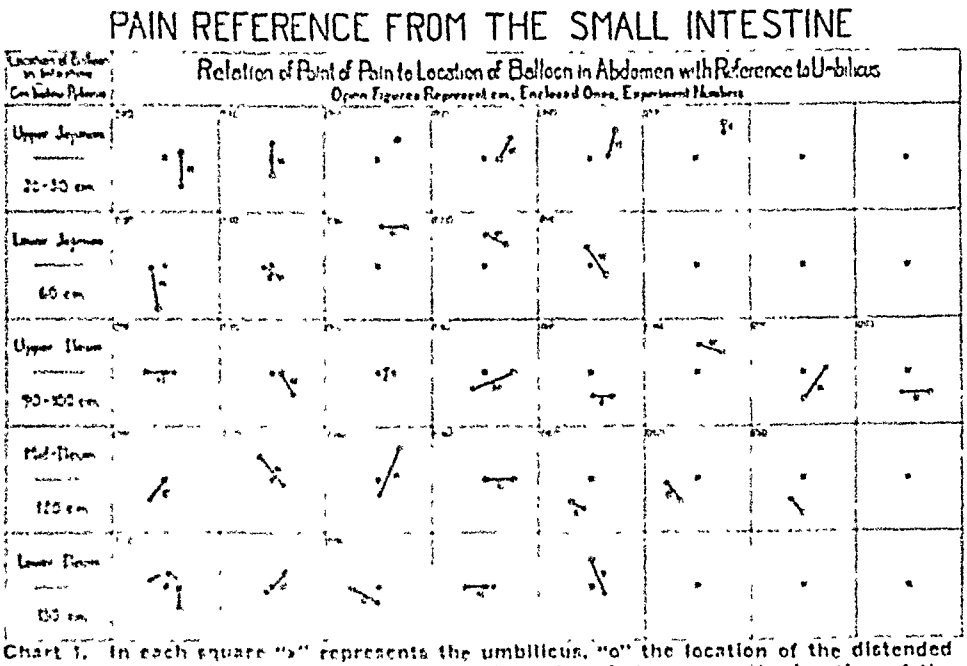


Chart 1. In each square "x" represents the umbilicus, "o" the location of the distended balloon in its relation to the umbilicus and the point of the arrow, the location of the pain. The figures at the middle of the straight lines represent the distance in cm. from the balloon to the point of pain.

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DISCUSSION

DR. MAX EINHORN (New York City): I am very glad that Dr. Miller took pains to walk in the line which I tried to open up in 1910. Shortly after devising the tube, the duodenal tube, I tried right away first to have an obturator at the end of the tube and then an aspirating arrangement above it so that we should be able to examine, for instance, the duodenal contents separately and also to have X-ray pictures taken which Dr. Stewart at that time tried. I think it must have been 1912 or 1913, I do not know exactly.

Later on I made another attempt to investigate a small piece of the intestinal tract to localize it, having a three-cannula tube and obturator on the end and on the proximal side and in the middle a place for aspiration so that we could limit ourselves to a certain piece of the intestinal tract for separate investigation. I knew that certain experiments had been done but my intention was to give a method which could be practiced on patients.

Dr. McCafferty, who is still living, was the man on whom I have tried that method successfully. I was able to cut off the stomach, the duodenum, and localize a piece of the intestine so that the juice could be examined. I got the juice at that time. We could also localize, for instance, the papilla, cutting off a little ahead of the papilla and a few centimeters below.

But this instrument while it is all right to examine, interested me simply as a new way of doing something. However, I could not keep myself busy all the time with these experiments, or I would not have the time to treat patients. I had more important things to do than these experiments.

As to the intestinal tube, I tried right from the start to see how deep we could enter. There were all kinds of methods until I ultimately succeeded in having the tubes going down the entire intestinal tract. The tube which I found was the best for this purpose was an intestinal tube by means of which we can make the tube go into the caecum; but we can let it go through the entire intestinal tract. Here is a picture (showing printed pamphlet with illustration) of a patient who was treated at that time for ulcerative colitis. The tube went in further and we were able at that time to examine the intestinal contents of the descending colon.

Dr. Coleman and Dr. Thomson, a lady physician, helped me to carry out these investigations of the bacteria in the different regions of the intestine. This that I show you was published in about 1930, with the results of those examinations.

The difficulty is if we go with the tube away down into the intestine or the large bowel there is always contamination. It was necessary to seal up the tube first before we made the examination. We had to arrange for a collodion paraffin mixture which afterwards had to be tied up with a rubber band and then that tube could be sterilized. When we reached a certain depth in the intestine where we wanted to examine the bacteria it was opened and the intestinal contents aspirated. It would take too much time to go into the details of that.

I am very grateful to Dr. Miller that he took up these things again. If he says that it could go in in two or three hours and go away down, that I could not do. I think the physiological aspects point to the fact that we cannot do it as quickly as that. It would be an advantage, but I think if we want to examine things as they are we had better keep to the physiologic factor and act accordingly.

DR. LEWIS GREGORY COLE (New York City): I have just two points to make. One of them is merely of historical interest. We used a double tube with a balloon on the end to cause artificial dilitation of the duodenum and to wall of certain sections of the small intestinal tract. This was reported and illustrated in the Archives of Roentgenology in 1911.

The other point was a stunt that we used to enable the patient to swallow the tube with the collapsed balloon. We found that by sewing this balloon into an oyster and then having the patient swallow it, we often had little or no trouble.

DR. ANTON OELGOETZ (Columbus, Ohio, by invitation): I should like to emphasize the ingeniousness and practicability of this tube. We have been interested in obtaining the total pancreatic secretion. We attempted to get down to various levels of the bowel with single-lumen tubes, but until we had some correspondence with Dr. Abbott, we were unsuccessful. However, since then it has been very easy.

The first thing about this tube is that you can produce a temporary obstruction at any desired level of the bowel by inflating the balloon. We found the two-lumen tube the most useful. We only use the three-lumen tube to obtain secretions, simultaneously, from different levels of the bowel. This maneuver produced some very interesting results concerning digestion which we are going to report a little later.

This tube looks a trifle large. When you first look at it, it appears that the patient will have a terrifically difficult time swallowing it. But as a matter of fact, it is very easy. The smaller the diameter of the tube, the more difficult it is for the oesophagus and the bowel to grasp it by peristalsis. With this tube you can actually feel the tug of peristalsis. Most of our patients hardly gagged, whereas smaller tubes caused a lot of gagging.

We were especially interested in the rate of digestion of proteins and carbohydrates. We gave measured quantities of carbohydrates after passing the tube, and then withdrew secretions from various levels of the bowel at measured intervals. By starting at the ileum and withdrawing the tube a foot or so on successive days, we were able to determine how far down the bowel a given quantity of carbohydrate gets, before it is entirely digested, and how far down the resulting sugar gets before it is completely absorbed. We have done this same thing with measured quantities of protein.

In our experience this tube either goes through the pylorus very easily or it won't go through at all. Recently, we found it helpful to dip about two feet of the distal end of the tube into a thick solution of gelatine, which stiffens the tube. By the time the tube reaches the stomach, it softens, but still retains enough stiffness to enable one to push it through the pylorus.

Dr. Einhorn said that he was doubtful of the tube because he couldn't get it down. We had no difficulty in getting the tube to any desired level of the bowel, but at first, we were a little afraid of how to get it out again. When you get the tube far down in the bowel, as this picture showed, it appears as if the tube would act like a drawstring when you remove it, drawing the bowel into a knot and preventing removal of the tube. But it doesn't do this; it withdraws as easily as a duodenal tube. This tube is an ingenious method for finding out some hitherto unknown things about the intestinal tract at its different levels: pH at different levels and at different periods of the digestive cycle, bacterial content, enzyme concentration, where and when absorption takes place, and so forth.

DR. T. GRIER MILLER (Philadelphia, Pa., closing the discussion): I merely wish to thank these gentlemen for their kindness in discusing our paper. I really think it is hardly worth while at this time going into the part of the paper which the time limit did not permit me to present in full. I thank you very much.

The Components of the Gastric Secretion*

By

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I HAVE been invited to speak to you today about the components of the gastric secretion, particularly with reference to my own contributions to the subject. Shortly after starting work in this field of investigation, I made a systematic search of its periodical literature. In the course of this task, three broad considerations came to assume dominant importance in my mind, and I should like to discuss them briefly at the outset.

First, the number of articles dealing more or less directly with this subject was tremendous. At the present time, my bibliography file contains well over a thousand such references — apart from an even greater number which deal with other aspects of gastric physiology. This literature is for the most part a confused mass of inadequate data, obtained by inaccurate analytical methods, and based on impure material such as stomach contents contaminated by saliva and duodenal fluids. Even material obtained in sham feeding or stomach pouch experiments was usually collected in such a way as to permit of contamination by blood from traumatized mucosa and by serous exudate from eroded areas around the mouth of the pouch. Although such quantitative studies ought to be carried out with physico-chemical precision, it seemed as if every investigator had made more or less the same observations in the same inaccurate way. As for the generalizations based on this work, it was amazing to see how frequently the conclusions were entirely unrelated logically to the observations from which they were supposed to have been deduced. Very often, the conclusions of several workers were diametrically opposite, although their data indicated no significant discrepancy. Such confusion might have been avoided effectively by statistical treatment of the data, but rigorous analyses of the observations were a rarity.

In the *second place*, and in consequence of this frequent lack of logical connection between data and conclusion, I found very few quantitative generalizations which were universally accepted. On the whole, opinion seemed to be divided into two camps. One of these supported the Pavlov theory,† which maintained that the acidity of gastric juice tends to be constant, and that the observed variations results from partial neutralization by mucus. The other group supported the Rosemann theory which maintained that the total chloride concentration rather than the acidity is the constant factor, because neutral chloride at fixed concentration is secreted as a precursor which undergoes partial hydrolysis to HCl. According to the latter view, increased intensity of stimulus results in an increased concentration of acid and a decreased concentration of neutral chloride. In spite of the sharp line which differentiates these mutually contradictory theories, neither had been proved conclusively in the course of a quarter of a century of research.

Finally, gastric juice was always thought of as if it were only a mixture of many chemical substances from a single source—the gastric mucosa. Although it was generally known that these substances came from several different kinds of secretory cells, very little consideration was given to their separate physiological origins. Investigators were concerned more with the chemistry of mixed gastric juice than with the chemistry of the individual secretions and their mutual interactions. During the last decade, however, emphasis has shifted perceptibly from the chemical entities to the physiological entities which constitute the mixed gastric secretion, and my own work is a manifestation of this different point of view. From this aspect, therefore, the components of the gastric secretion are defined as the individual fluids formed by at least four different types of secretory cell in the gastric mucosa.

From these considerations it was apparent that my own approach to the problem of the nature of the component secretions must be based on (1) a technique for collecting gastric juice of the very highest purity, (2) analytical methods of fairly high precision, (3) statistical treatment of the data wherever it is required, and above all (4) formulation of experiments with reference to the individual secretions and not to mixed gastric juice. Attention to these matters has already resulted in considerable clarification of the subject.

HISTORICAL CONSIDERATIONS

Before proceeding to the details of these results, however, I should like to review very briefly the major histological considerations of our subject. In spite of the variety of names associated with some of the gland cells, it is now generally accepted that the gastric mucosa contains four major types of secretory cell, which may occur in slightly modified form in different regions of the stomach. These cells and their secretory products are as follows: (1) The *mucous cells* of the surface epithelium, which give rise to viscous mucus and, on coagulation of the latter to the familiar strings and clots of mucin. (2) The *peptic cells* (also called *body chief, central* or *adelomorphous cells*) which secrete the enzymes. (3) The *parietal cells* (also known as *Belegzellen, acid, oxyntic*, and *delomorphous cells*) which contribute the HCl. (4) The *neck chief cells*, the product from which is unknown, though it may be a mucoid secretion according to Babkin (1931). The chemical composition of these secretions was entirely unknown, except for the one substance which served to characterize each of them. Also, apart from the unproved theories of Pavlov and Rosemann, nothing definite was known about the cellular source of the

*From Columbia University Medical Center, New York City.
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†For a detailed analysis of these two theories see Hollander (1934, b).
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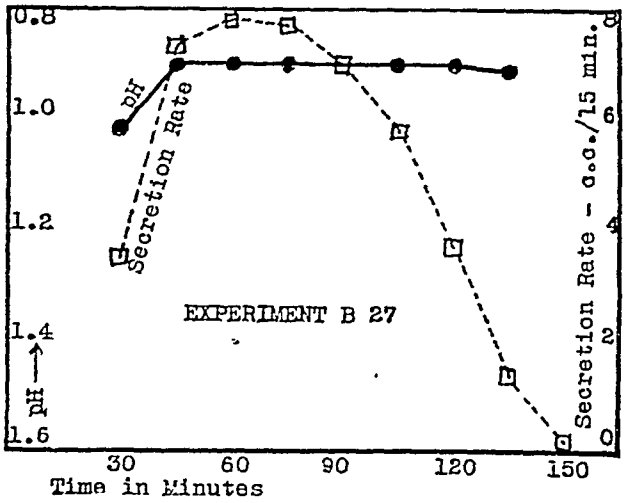


Fig. 1. Simultaneous rate and acidity (pH) curves, showing the attainment of constant acidity in spite of a marked rise and fall in rate of secretion. From a histamine experiment on a fundic pouch dog. (Hollander and Cowgill, 1931).

base, phosphate, protein buffer, etc., which are always present in gastric juice. Had it been possible to collect each individual secretion in the pure state by some micro-pipetting technique, such as that of Chambers for unicellular organisms or A. N. Richards for the kidney, the problem would have been relatively simple. Unfortunately, no such technique was possible and so it became necessary to develop an indirect approach in this search for the chemical composition of the individual secretions.

In keeping with the criticism which I made before regarding the use of impure gastric juice by other investigators, the first step in this work was the development of a technique for collecting gastric juice of the highest possible purity from Pavlov and Heidenhain pouch dogs; *i.e.*, juice which is free, not only of food, saliva, and regurgitated duodenal contents—such as is obtained in the ordinary gastric pouch technique—but which contains neither blood from injured mucosa, exudate from eroded skin and muscle, nor more than minimal amounts of mucin. Such a technique evolved in collaboration with Dr. G. R. Cowgill (Hollander and Cowgill, 1931), was based on the surgical development of a sphincter at the mouth of the pouch. By this method, the digestive fluid was retained in the pouch until it could be drawn off by temporary insertion of a small rubber catheter. Periodic removal of the accumulated juice prevented its leaking out continuously and thus eroding the abdominal wall surrounding the pouch opening. Furthermore, in collecting the juice for study, the sphincter obviated the use of hard rubber or metallic devices which cause considerable irritation and even injury to the pouch lining, thereby preventing contamination of the fluid with blood and excessive amounts of mucus. The gastric juice obtained by this technique was usually so clear and colorless that it might have been mistaken for ordinary distilled water. In addition to this collection technique, a special method was developed for analyzing the analytical data obtained from this material. This mathematical procedure involved the statistical treatment of a large series of samples of varying acidity; and it was based on a mathematical process known as "extrapolation," whereby it is possible under certain conditions to infer the composition of a sample of juice whose acidity value is higher or lower than any actually included in the original data.

Lack of time prevents my going into all the detailed results of this series of investigations, and so I shall touch merely on several of the high spots throughout the work.

(1) Previous investigators, almost without exception, had found that, in any one experiment, the acidity of gastric pouch juice rises and falls with the volume-rate of secretion, whether the stimulus be food or histamine. However, this parallelism of acidity and rate curves was cited by the proponents of both the Pavlov and Rosemann theories in support of their respective views. Under ordinary conditions of collecting the secretion, I also was able to confirm this observation, but when juice was collected by means of the sphincter technique I found that the parallelism no longer exists in the absence of irritating objects. This finding was verified independently by constructing a collecting device from a small, soft rubber catheter. With this contrivance and a relatively rapid flow of juice to lubricate the surface of contact between catheter and mucosa, it was found that the acidity rose to a maximum shortly after the beginning of an experiment and stayed there to the very end, even though the rate of secretion fell off in the usual way. Figure 1 is an excellent illustration of this independence of acidity and rate of flow of secretion, an observation which definitely proves the theory of Pavlov. The pH of this "constant acidity" juice was in the neighborhood of 0.9, or about 160 millimoles—which is numerically the same as clinical units (Hollander and Cowgill, 1931).

(2) Let us next consider the neutral chloride con-

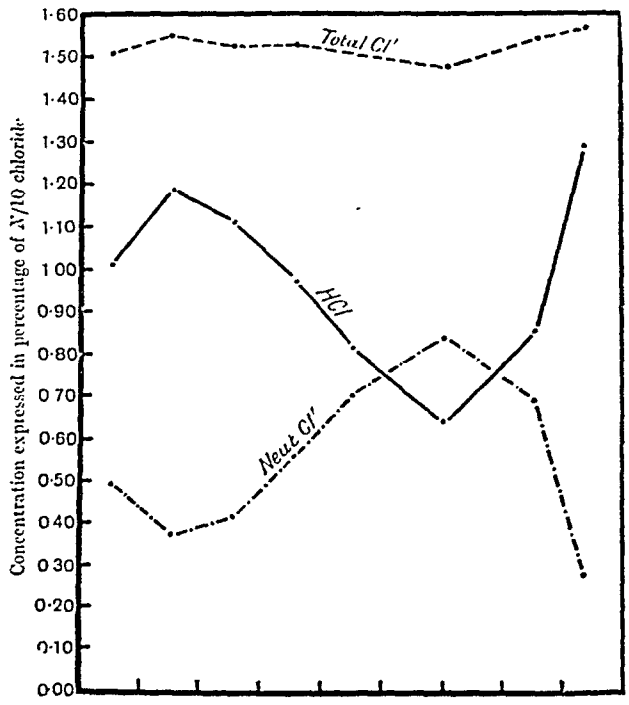


Fig. 1. Curves obtained from the secretion of an isolated gastric pouch in dog No. 1.

Fig. 2. Simultaneous acidity and neutral chloride curves, illustrating the inverse relation between these variables. (MacLean, Griffiths and Williams, 1928).

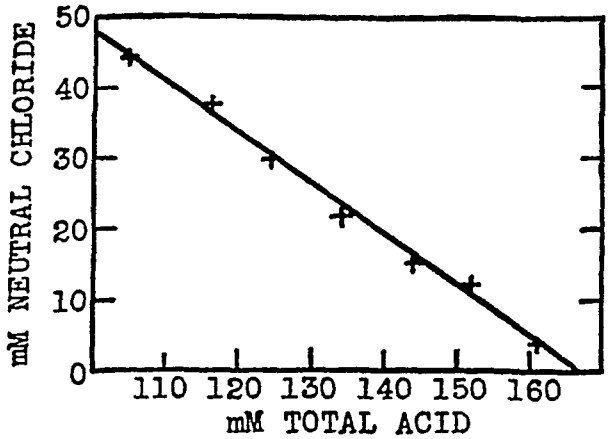


Fig. 3. Graph of neutral chloride and acidity data from 121 samples of pure mixed gastric secretion, treated statistically. The acidity intercept of this straight line, obtained by extrapolation, corresponds to pure parietal secretion with an acidity of 167 mm. and a neutral chloride concentration of zero. (Hollander, 1932).

tent of gastric juice, particularly in relation to its acidity. On this point also workers of the two schools were in agreement, *i.e.*, the concentration of neutral chloride always varies inversely with the HCl concentration. As the acidity rises, in any one experiment, the neutral chloride content falls, and as the acidity falls the other rises. This relation also was interpreted by each school to conform to its own views. A good illustration of this inverse relation, taken from a paper by MacLean, Griffiths, and Williams (1928) is given in Figure 2. My own observations have confirmed this fully. Indeed, in the case of the "constant acidity" juice, wherein the acidity values were as high as 150-160 mm., it frequently happened that the neutral chloride concentration was as low as 5-10 mm. This suggested that "constant acidity" juice might be almost, but not quite, pure parietal secretion; and that the latter, if it could be collected in a state of absolute purity, would be found to contain no neutral chloride whatever.

To test out this possibility, the mathematical technique referred to above was devised, and Figure 3 illustrates one of the experiments conducted for the purpose (Hollander, 1932). In this illustration over 120 samples of gastric juice of different acidities were collected from 5 different dogs. Each point on the graph represents an average of 10 to 20 of these samples, possessing nearly the same acidity; *i.e.*, its chloride and acidity values are averages of those for all the samples which it represents. Thus, instead of following the usual procedure and plotting both acidity and chloride values against the time of collection, as in Figure 2, I plotted the two concentrations directly against each other, as in Figure 3. The resulting graph was (statistically) a straight line, a result which was confirmed by several other series of observations. This straight line was then extended for a short distance beyond the last point, which corresponds to the specimens of "constant acidity" juice—a mathematical process known as *extrapolation*. In this case the line was extrapolated or extended downward until it crossed the acidity axis; the point of crossing is designated as the *acidity intercept* of the line. The theoretical specimen of gastric juice which corresponds to this intercept possesses a neutral chloride value of zero and an acidity of 167 mm. In the other experiments similar to this one, the acidity value of the intercept varied between 163 and 173 mm. These results were interpreted to mean that the gastric juice corresponding to these intercept values is the *ideally pure parietal secretion*, that this secretion is entirely free of neutral chloride, that its concentration of HCl is about 170 mm., and that "constant acidity" juice is this pure parietal fluid contaminated by small amounts of the other secretions from the gastric mucosa.

(3) Since the concentration of HCl in pure parietal secretion is *circa* 170 mm., and its neutral chloride content is zero, I next proceeded to investigate by a similar extrapolation technique, a number of the other chemical substances present in gastric juice (Hollander, 1934, a). Omitting all details of this study, it was found that the concentrations of combined acid, organic phosphorus, inorganic phosphate, and both inorganic and organic solids are all practically zero. Furthermore, it was shown that an HCl solution of *circa* 170 mm. concentration is isotonic with blood plasma, within the normal limits of experimental variation. Subsequently, Gilman and Cowgill (1933) showed that variations in blood osmotic pressure were actually paralleled by corresponding variations in osmotic pressure and chloride concentration of the gastric juice. In short, pure parietal secretion is an isotonic solution of practically pure hydrochloric acid. Its acid-base composition is represented by the first of the diagrams in Figure 4.

(4) Having shown that the parietal fluid contains only HCl, and that at a relatively constant concentration, the next problem was to determine the source of all the other chemical substances in mixed gastric juice and thus also the mechanism by which the ordinary variations in acid and neutral chloride concentration of pouch juice are brought about. In the case of the intact stomach, Boldyreff had advanced a theory based on the regurgitation of duodenal contents—an explanation which of late appears to be losing support among investigators. Since duodenal contents obviously cannot enter an isolated pouch, we are forced to infer that the effective agent in this situation is a non-acid fluid which is formed by the gastric mucosa itself. This fluid must supply the base which is present in the mixed secretion, in part as chloride and in part combined with the several buffer anions: phosphate, protein, and probably also bicar-

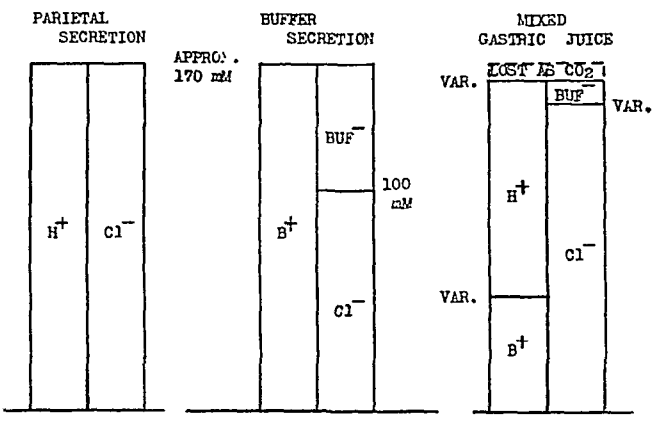


Fig. 4. Diagrams illustrating the acid-base composition of parietal secretion, buffer secretion and pure gastric juice formed by mixing the two secretions in variable proportions.

bonate which is lost as carbon dioxide on addition of acid.

The formation of such a non-acid fluid by both fundus and pyloric mucosa is well substantiated by the observations of Mitchell (1931), Martin (1932) and many others, and it seems very likely that this fluid is actually a specific buffer-containing secretion. As with the parietal secretion, no method was available for obtaining this fluid directly, but by means of the extrapolation method applied to a three coordinate system, and the data used for the previous study on the acid secretion, it was possible to arrive at a preliminary estimation of its chemical composition indirectly (Hollander, 1932). In this way it was suggested that the buffer secretion may be an isotonic mixture of neutral chloride and several buffer salts, and thus similar to blood plasma in its acid-base composition. The total concentration of base was placed around 170 mm., the chloride concentration about 100 mm., and the total buffer anion concentration about 70 mm.—as indicated in the second diagram in Figure 4. However, because of certain mathematical considerations, this extrapolation was not very reliable and the indicated composition was presented as a working hypothesis rather than an established fact. Subsequently, however, Wilhelmj and his associates (1934, 1935) reported that the chloride concentration of the non-acid secretion from dogs' pyloric and whole stomach pouches is 101 mm. on the average; its average concentration of buffer anion is 40 mm., but values as high as 80 and 90 were obtained. Also, Bolton and Goodhart (1931) reported a minimum chloride value of 99 mm. for the non-acid component from the fundus juice of cats. This evidence lends ample support to my earlier prediction regarding the similarity in acid-base composition between the buffer secretion and the blood plasma, but much work remains to be done before this similarity is established conclusively.

It follows from the foregoing, therefore, that in any sample of mixed gastric juice (see the third diagram in figure IV) the sum of the concentrations of total base (B+) and total acid (H+) will be equal to the sum of the concentrations of chloride (Cl—) and buffer anion (BUF—). Both of these sums will be less than the isotonic concentration (*circa* 170 mm.) by an amount equal to the amount of acid which was lost as H_2CO_3 or CO_2. In no case can the chloride concentration in gastric juice fall below that of the buffer secretion, about 100 mm., unless it be through the agency of some other fluid. In any particular sample of gastric juice, the relative values for the concentrations of HCl and neutral chloride will depend on the relative volumes of the parietal and buffer secretions. It must be added, however, that only part of the neutral chloride content of mixed gastric secretion arises by neutralization of the acid and the buffer salts; the larger portion exists as such in the non-acid fluid. Also, in addition to their chemical interaction, these two secretions exert a mutual diluting effect which serves further to reduce the concentrations of their respective constituents.

A final word concerning the source of this buffer-containing fluid. Originally, Pavlov postulated that ordinary deviations from constant acidity were the result of admixture of mucus secretion. In the absence of evidence to the contrary, this viscous fluid must still be admitted as a possible source of the buffer salts. However, my own experience has indicated that variations in the acidity of pouch juice may occur in the almost complete absence of mucin and therefore of the viscous mucous secretion. For this reason, it seems much more likely that the major part of the buffer-containing fluid arises as an independent secretion, which is identical with the dilution secretion (Verdünnungs-sekretion) of previous investigators. It is even possible that the mucoid secretion of Babkin (*vide supra*) and his associates, Webster and Komarov, (1932) is likewise identical with these, and that the source of the buffer secretion is the neck chief cells of the gastric tubules.

To summarize: Pure gastric juice is a mixture of at least four independent secretions from the gastric glands. As yet we know nothing about the chemical composition of the secretions from the peptic and mucous cells. The parietal secretion has been shown to be an isotonic solution of practically pure hydrochloric acid, thus finally resolving the old Pavlov-Rosemann controversy regarding the constancy of the gastric acidity in favor of the former. This is the first of the digestive secretions for which the chemical composition has been established. The normal variations in the acid and neutral chloride concentrations of pouch juice are caused by a buffer-containing secretion which acts by both neutralization and dilution of the parietal fluid. It is suggested that the chemical composition of this buffer secretion is probably similar to that of blood plasma, so far as its inorganic constituents are concerned. Furthermore, it is probably identical with the dilution secretion of other investigators, and perhaps also with the mucoid secretion of Babkin and his associates. Finally, I believe that we already have sufficient evidence to show that the buffer secretion plays a major role as an intragastric agent in the normal control of gastric acidity—more important even than duodenal regurgitation as an extragastric agent. As such, this secretion is of tremendous importance to clinicians and physiologists alike, and it deserves extensive investigation by both.

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DISCUSSION

DR. WALTER C. ALVAREZ (Rochester, Minnesota): I do not feel quite qualified to discuss such a technical chemical subject with my poor knowledge of chemistry. But, I will say this as one interested in physiology, it seemed to me for years that we were floundering around, many of us trying to learn something about gastric secretion, using juice from the stomachs of human beings, mixed with food. God knows gastric juice is complicated enough without adding mixtures of food and whatnot to it.

Imagine that this arm and hand of mine represent a gastric gland. Here near the bottom are the chief cells. Nearer the mouth of the gland are the mucoid cells; outside of these cells are the parietal cells. As a physiologist,

I would like to know what are the secretions of these several cells.

In the gastric juice one finds acid, pepsin, mucous, and other substances. Where did they come from? Which of the cells produced which ones of the different constituents?

For years it seemed to me that we physicians were floundering around in a morass of ignorance because we were ignoring the need for answering these important and basic questions. Then, one day I happened to pick up the Journal of Biologic Chemistry for January, 1934. There I found an article by a man whom I did not know. In that article there was light on the subject of gastric acidity and plenty of it. At there was the beginning of an answer to the questions that had been in my mind.

As I commonly do when a man's writings greatly please me, I promptly made a pilgrimage to see him and found him to be a real fellow. His work and his thoughts expressed in letters have been a big stimulus to me ever since. I wish he could get back to this work on gastric juice because he has the mental equipment and the technical training with which to tackle the problems as I think they should be tackled.

Now, why am I so interested in learning exact details as to the secretion of the gastric juice? Because, as someone who has to treat peptic ulcer, I want to learn how to cut down the secretion of acid. How happy we physicians would be if we could produce even temporarily hypo or anacidity in patients with ulcer; then many of our troubles would be over.

We want to throw a monkey wrench into the machinery of acid formation, but where are we to put it until we know every stage in the production of the acid; until we know the chemical processes that go on, and how those processes are linked up with varying conditions in the blood, such as the amount of CO_2, chlorides, etc. When we know all these details then we may see a place in which the insertion of a small monkey wrench can have a big effect in decreasing the secretion of gastric acid.

DR. FRANKLIN HOLLANDER (closing the discussion): There is one particular point which I should like to emphasize in closing. The idea of a non-acid gastric secretion, of course, is far from being new. However, as this concept has usually been advanced, it involves a secretion which contains only neutral chlorides but no buffer salts; that is, a fluid which causes the ordinary variations in gastric acidity solely by a process of dilution. Now, the chief objection to this theory which has been raised in the past is this, that there is as yet no evidence to indicate that such a fluid can be secreted in sufficient quantity to be effective as an agent in the intragastric control of the acidity. I think the present is an opportune time to answer this argument.

In the first place, proponents of an extra-gastric mechanism of acidity regulation have sponsored Boldyreff's theory of duodenal regurgitation. But no such mechanism can operate in the isolated stomach pouch. Nevertheless, quantitative variations in acidity and neutral chloride content can be observed to practically the same extent in pouches as in intact stomachs. It follows, therefore, that since such reductions in acidity can occur in the pouch without the aid of an extra-gastric mechanism, there is no need for our invoking one in the case of the entire unoperated stomach. In other words, there must be some intragastric secretory agent which is elaborated in sufficient quantity to act in this way.

In the second place, the non-acid secretion which I have described today differs from the older notion of a dilution secretion in this respect, that it functions as an agent of acidity regulation, not only by dilution, but also by a process of neutralization. Consequently, comparing it with an equal volume of the simple dilution secretion, the reduction in acidity effected by the former will be considerably greater than that caused by dilution alone. In other words, the buffer secretion is more efficient and therefore even less of it is required to regulate the acidity than of the other.

Of course, complete refutation of all arguments against the existence of this buffer secretion must rest ultimately on its actual isolation and our learning more about it, particularly the stimulatory mechanism by which it is formed in the normal course of digestion.

Gastric Secretory Behavior in Chronic Gastritis*

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THERE are many who feel with Hurst, Faber and Konjetzny, Henning and Schindler that gastritis is the most common stomach disorder. Great difficulties are encountered when an effort is made to diagnose or classify cases of gastritis, which have not been proved by gross and microscopic study of operation-room material. Only those cases associated with ulcer and cancer have had world-wide scrutiny and even in these the assumption of a primary gastritis has not been proved.† Stomachs examined at autopsy, which have not been treated immediately after death by the Faber formalin method, are of little value for pathological study, and that method is little used. There remains that large group of patients upon whom a tentative diagnosis of gastritis is entertained whose stomachs should not be removed by the surgeon and who do not go to necropsy. A clinical suspicion of gastritis, based upon the existence of possible etiological factors, can only be confirmed by analysis of the

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†Cases of proven gastritis in association with ulcer and cancer have purposely been omitted. The secretory behavior of this group will be the subject of a later paper.

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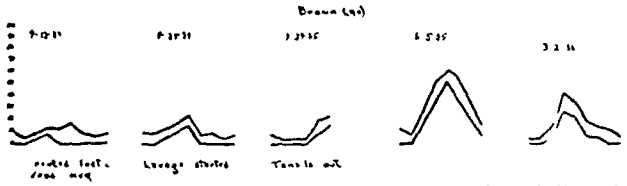


Fig. 1, Case 1. Marked improvement in gastric acidity following treatment for lues, gastric lavage and tonsillectomy.

stomach contents, the gastroscope and study of the mucosal pattern by X-ray. Unfortunately interpretation based upon any of these methods is subject to considerable error. There is great need for standardization and comparisons of the methods of diagnosis in cases followed for long periods. It is for this reason that we offer no apology for presenting a group of cases, in many of which the diagnosis of gastritis is not surely established, for critical review of the secretory findings. Most cases presented have been examined gastroscopically, and unquestionably in the light of our present knowledge many would make an unequivocal diagnosis of gastritis. We purposely omit the gastroscopic findings until we feel, with our endoscopist, Doctor Tucker, more certain of the gastroscopic diagnosis. X-ray studies of the mucosal pattern have been routinely carried out and indications of gastritis in the light of more recent work were frequently present, although they were not always pathognomonic.

The cases share commonly evidences of a "dirty stomach," *i.e.*, excessive gastric sediment in the fasting and lavaged stomach which microscopically showed large amounts of mucus, pus, bacteria and exfoliated gastric epithelium. The residua were always examined by one of us and not by inexperienced technicians. We realize, of course, that cases of gastritis may show no evidence of exudation, desquamation and infection by this method and likewise that the personal equation in the interpretation of the findings is considerable.

In 18 cases special tissue block sections were prepared from the gastric sediment removed through the stomach tube by the method of Moffitt and the material stained, sectioned and studied in the same manner as pathological tissue sections. In only three of them, gastric tissue fragments were found which afforded an opportunity for detailed study. Although only 16 per cent of the cases examined in this way yielded satisfactory material for study, we feel that the method may prove a valuable adjunct in the diagnosis of gastritis. (Foot Note).

Foot Note *Technique of sectioning sediment of gastric washings* After recording the gross description and amount of the fluid a small quantity is placed upon a slide and observed to determine whether there is enough mucus or other viscid matter present to allow the sediment to form the necessary firm mass when acted upon by formaldehyde and also to obtain information in regard to the character of the sediment, whether mucoid, hemorrhagic, biliary, amorphous or granular, for it is necessary, in case of the latter two, to add a little gelatin to hold the amorphous or granular matter in a mass.

One drop of ten per cent gelatin solution is added to each two cubic centimeters of the fluid

The fluid is then centrifuged at a high rate of speed (about 4000 revolutions per minute) for one-half hour. This causes the sediment to be tightly packed in the bottom of the tube The supernatent fluid is discarded and the tube filled with 6% formaldehyde (15% formaline).

A narrow, flat, flexible applicator is passed about the plug of sediment to loosen it from the glass so that the hardening action of the formaldehyde will begin promptly.

The formaldehyde is allowed to act upon the sediment for a week being changed at the end of twenty-four hours and once or twice later

The hardened sediment caked in the bottom of the tube is worked loose by means of the metal applicator taking care not to break it. It is then treated as though it were a section of tissue—passed through the alcohols, ether and absolute alcohol, thin celloidin, thick celloidin, mounted in celloidin, sectioned and stained with haematoxylin and eosin.

Celloidin is used in preference to paraffin as granular sediments generally drop out during sectioning when the latter is used

Any floating mucoid masses which do not centrifuge to the bottom of the tube—and these are quite frequently encountered—are treated just as are the hardened sediment masses

The group of cases selected permit a study of secretory behavior over long periods or illustrate changes in secretory status of particular interest. A lengthy period of observation in a few cases properly followed up should prove of more value than a much larger group followed for a briefer period of time. All of the secretory data have been obtained by the ordinary two-hour fractional gastric analysis, using the bread and water meal with or without histamine.

GROUP I—CASES OF POSSIBLE GASTRITIS WITH REDUCED OR ABSENT ACIDITY SHOWING INCREASED ACIDITY AFTER THERAPY

Practically all observers are agreed that there is a tendency toward reduction in gastric secretion as measured by gastric analysis in chronic progressive gastritis. Hurst attributes the reduced acidity to degenerative changes in the oxyntic cells, obstruction to the intracellular canaliculi by swollen cells and an excessive secretion of mucus which neutralizes the acid to a slight extent and blocks up the mouths of the secreting tubules. Henning found either hypo or anacidity in 68 per cent of stomachs showing evidences of chronic gastritis by gastroscopy. Faber feels that the development of achlorhydria is primarily dependent upon the gastritis per se and may develop in any stomach regardless of the previous acid level. Hurst favors a constitutional hypo-acid diathesis as an impor-

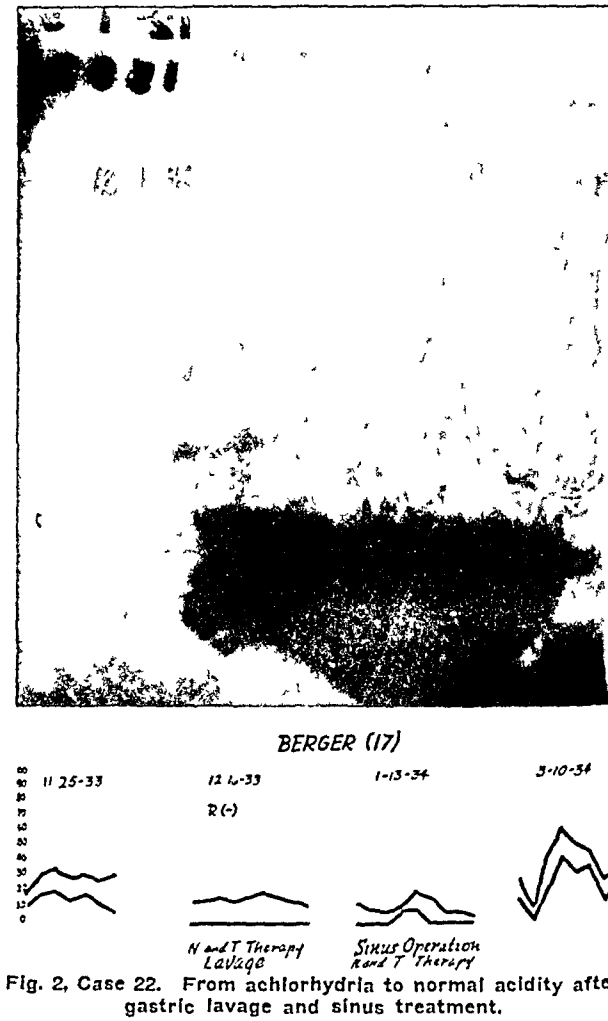


Fig. 2, Case 22. From achlorhydria to normal acidity after gastric lavage and sinus treatment.

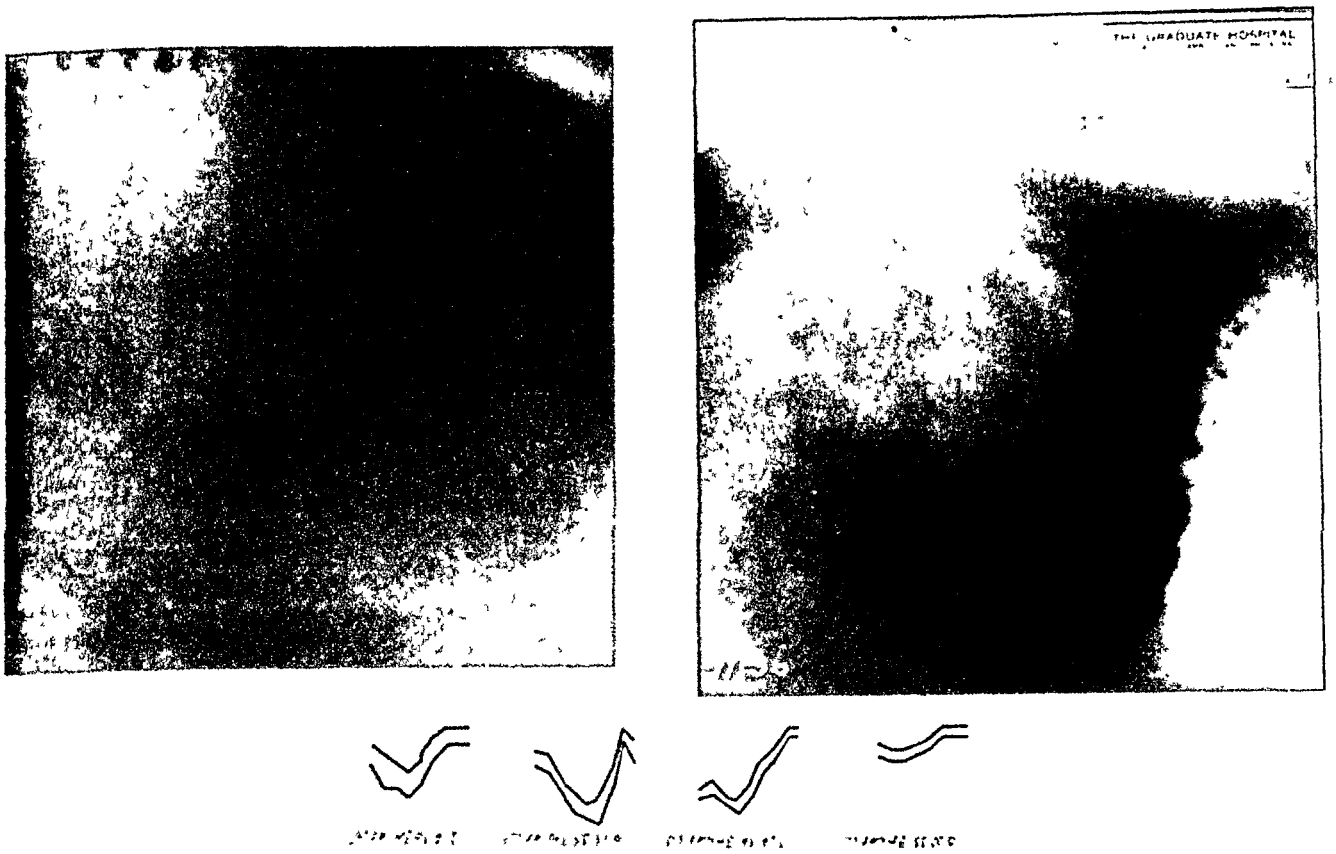


Fig. 3, Case 23. Dilated stomach gradually reduced in size with hypochlorydria changing to normal acidity during treatment for gastritis with lavage.

tant conditioning influence. He assumes that very near all individuals with the constitutional "hypo-acid diathesis" and a few with normal acid eventually develop achlorhydria as a result of gastritis, claiming that the "inborn" hypochlorhydria renders their stomach mucosa more liable to injury and permanent damage following insult.

Hurst claims to have brought about a return of acid in 80 per cent of his cases of achlorhydria by treatment directed toward gastritis. A group of cases has been selected to illustrate improvement in the secretory level following various therapeutic agents.

Case 1, V. B., a colored female, 39 years of age, was admitted September 12, 1933, because of early postprandial epigastric distress of two years' duration. Her Wassermann had recently become negative after treatment for a gumma of the sternum. Pertinent findings were a gastritis, right hypertension, obesity, mild hypothyroidism, diseased tonsils and dental caries. The sediment from the fasting and lavaged stomach suggested mucosal inflammation. The X-ray evidence of gastritis was not convincing. The acid curves from September, 1933, to January, 1935, showed an extreme hypochlorhydria. A normal acidity appeared in June, 1935, after 2 years of treatment, including antiluetic therapy from April, 1933, to June, 1934, gastritis management with frequent therapeutic lavage starting in August, 1934, and tonsillectomy in January, 1935, (Fig. 1).

Case 22, S. B., a white girl, 17 years old, showed a change in secretory status from an apparent achylia (without histamine) to normal acidity within 3 months after sinus drainage and nose and throat treatments (Fig. 2) for maxillary sinusitis and chronic ethmoiditis with postnasal discharge. Nausea, early postprandial distress, and anorexia disappeared with the return of acid and the patient gained in weight. The accompanying illustration shows an unusually smooth mucosal pattern. The gastric sediment was rich in cells, mucus and bacteria.

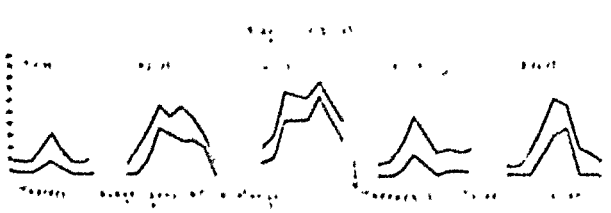


Fig. 4, Case 16. From hypochlorhydria to hyperacidity after gastric lavage and extraction of teeth with return to hypochlorhydria after discontinuing "gastritis" therapy.

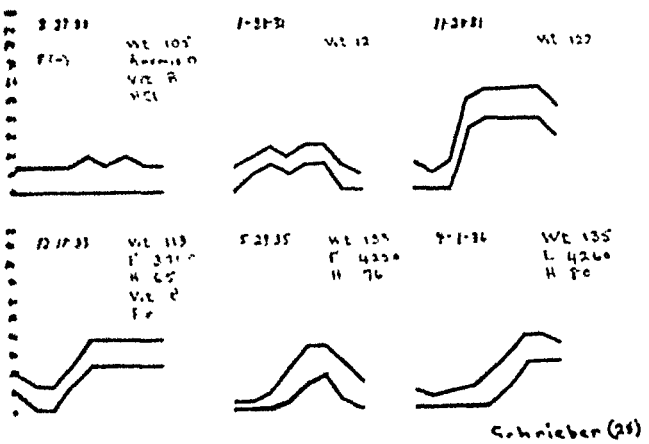


Fig. 5, Case 6. Achlorhydria to normal acidity with vitamine "B" and hydrochloric acid. Therapy discontinued with subsequent anemia and hypochlorhydria.

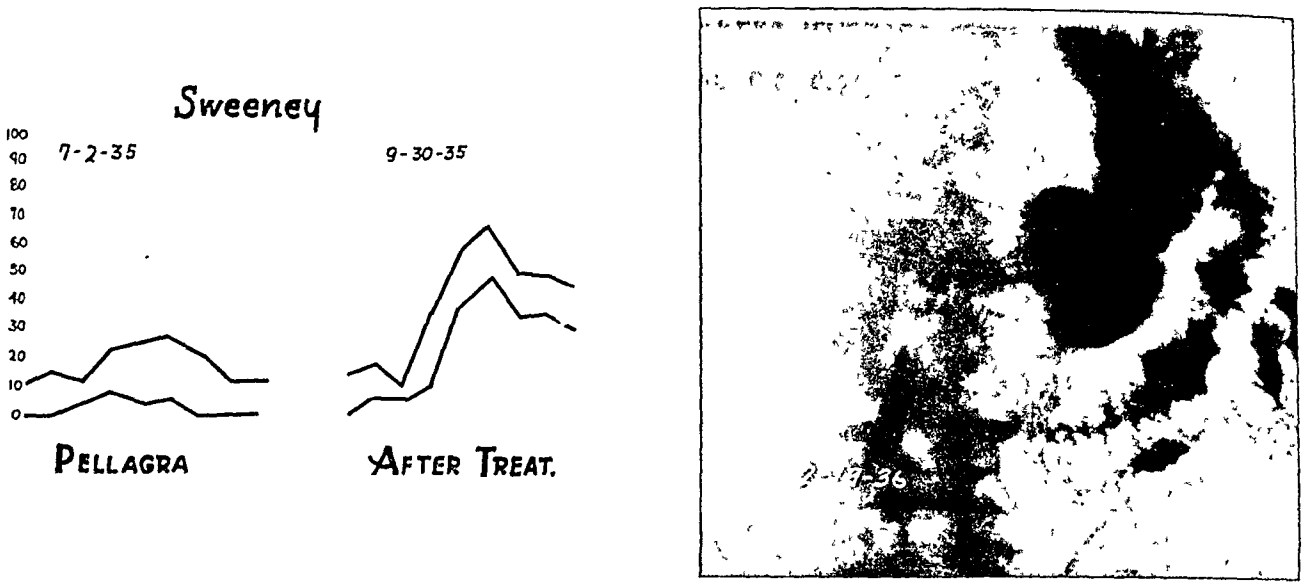


Fig. 6, Case 17. Hypochlorhydria to normal acidity in a pellagrin on vitamine "B."

Case 23, M. B., a colored female, 34 years of age, showed a tremendously dilated stomach without ascertainable cause and hypochlorhydria in June, 1933. Bouts of nausea and postprandial fullness had been recurring for several years. Studies revealed hypothyroidism and hypertension. Therapeutic lavage was given from April to September, 1933. The stomach gradually decreased in size and the gastric analysis showed a hyperacidity in July, 1934, (Fig. 3). Evidence of gastritis was suggested by examination of the stomach contents and study of the mucosal pattern.

Case 15, A. M., an Italian female of 21 years, showed an extreme hypochlorhydria in July, 1933. The acidity gradually mounted to a slight hyperacidity in 4 months (Fig. 4) following therapeutic gastric lavage and extraction of abscessed teeth. Re-examination after a year's absence from the clinic showed a lowering of acidity which started to mount a second time upon instituting glandular therapy for hypothyroidism. X-ray evidence of gastritis was lacking but the stomach residua were suggestive.

Case 6, H. S., an asthenic, under-nourished nurse of 25 years, shows an interesting type of secretory behavior during a six-year period (Fig. 5). In March, 1930, there was an apparent achylia (no histamine), the gastric residue containing many pus cells and phagocytes. The stomach films were unsatisfactory. Vitamine B, hydrochloric acid and a high caloric diet were followed by hypochlorhydria in January, 1931, and normal acidity in November, 1931. At this time the amount of cellular and mucoid sediment had increased. In December, 1933, after cessation of therapy, the acid curve was lower and a moderate anemia developed. In spite of iron and vitamine B with improvement in the blood-count, the acid curve was

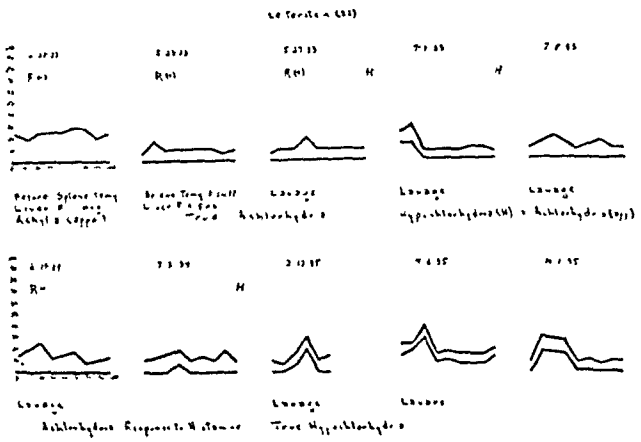


Fig. 7, Case 25. Apparent achylia to hypochlorhydria following splenectomy and "gastritis" therapy including lavage.

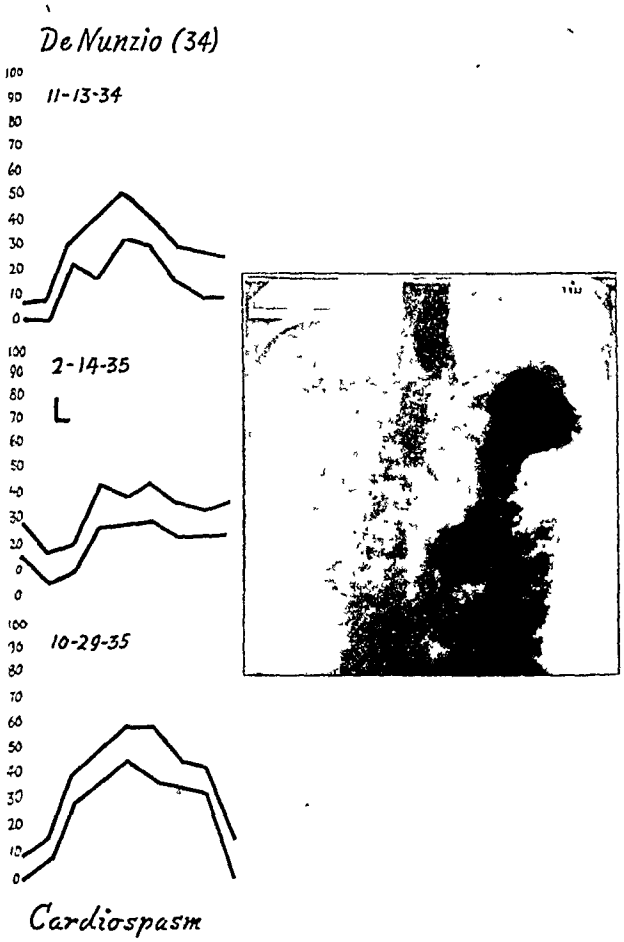


Fig. 8, Case 14. Cardiospasm with gastritis with desquamation of sizable mucosal fragments.

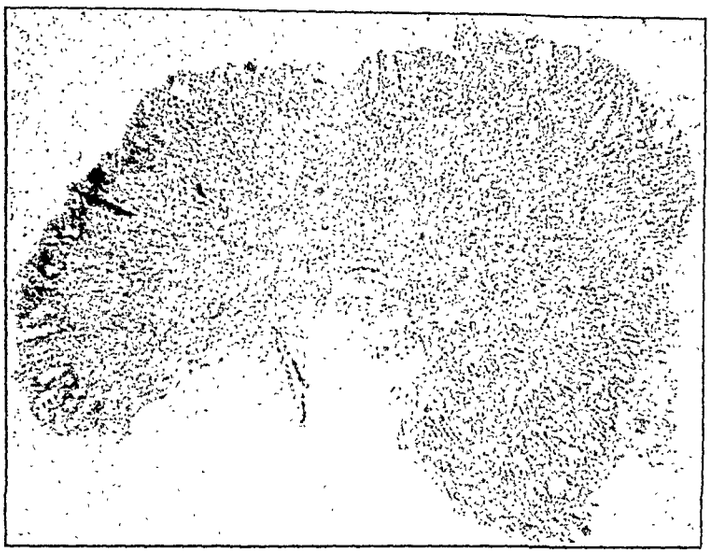


Fig. 9A, Case 14. Fragment of gastric mucosa (X32) aspirated through open tube gastroscope.

still lower in May, 1935, and remained low. X-ray in April, 1936, was very suggestive of gastritis. Etiological factors may have been diseased tonsils, frequent chronic "colds" and chronic constipation. The patient gained 30 pounds in weight during the six-year period.

Case 17, D. S., a typical alcoholic pellagrin, over 50 years of age, with evidence of multiple type of deficiency disorder is included to illustrate the return of gastric acidity to normal after administration of vitamin B. Liver was purposely withheld (Fig. 6).

Case 25, M. L., Jewish male, 22 years old, illustrates an improvement in secretory status following splenectomy for typical Banti's disease. The gastric analysis showed an apparent (no histamine) achylia previous to splenectomy (Fig. 7), which occurred March 24, 1933. Two months later gastric rennet was present but no acid after histamine injection. Tri-weekly gastric lavage was given from May until August, 1933. In early July, acid appeared only after histamine injection. In June, 1934, the gastric secretory status was the same (achlorhydria with ordinary meal and hypochlorhydria after histamine). From June, 1934, to May, 1935, bi-weekly gastric lavage was carried out. From February until October, 1935, the stomach secreted acid without histamine. The secretory status improved from an apparent achylia to a true hypochlorhydria after splenectomy.

Case 14, K. D., an Italian female, 34 years of age, is of



Fig. 9B, Case 14. High power (X200) of 9A showing signs of inflammation and degeneration of gastric mucosa.

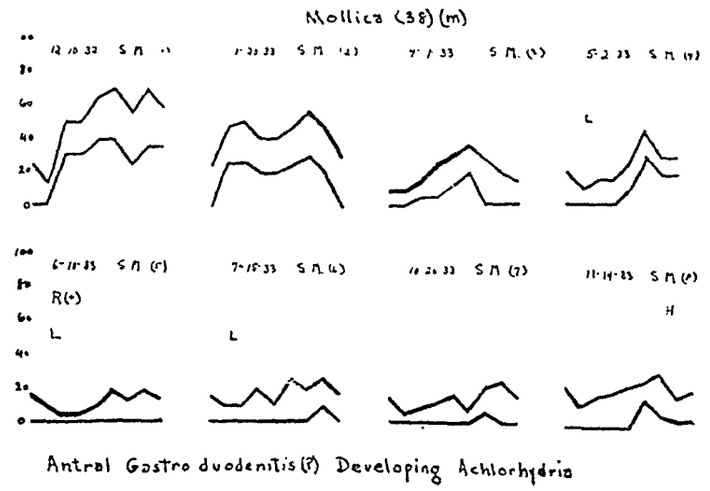


Fig. 10, Case 13. Probable gastro-duodenitis with normal acidity developing achlorhydria in spite of "gastritis" therapy.

special interest because of cardiospasm of four years duration with dilatation of the esophagus. She consumed alcohol in moderate amounts and had several abscessed teeth. The stomach films suggested a possible gastritis of the proximal one-third of the stomach. Gastric acidity changed from a slight hypochlorhydria to normal acidity during one year (Fig. 8). The gastric sediment showed excessive amounts of mucus, pus cells and bacteria. Material, aspirated through the open tube gastroscope and prepared by the method of Moffitt, yielded tissue fragments of sufficient size and character to justify a diagnosis of gastritis (Fig. 9).

Histological Description.—The section shows three fragments of gastric mucosa and hyaline blood clot. The surface epithelium of the mucosa is missing, being covered by a fibrinous exudate in some places and in others a thin cuticular border. The alveolae are dilated by retained mucus (goblet cells) and degenerated and their lumena filled with protoplasmic-cell remnants and mucus. Many of the nuclei at the bases of these cells have survived. The cells of the neck portions of the glands show no advanced changes. In the deeper portions of the glands, the cells of some are in fairly good condition while in others various degrees of cloudy swelling or albumenoid degeneration are observed. The chief cells are more affected than the parietal cells. In some areas the glands are fragmented and scattered about in the tunica propria. The tunica

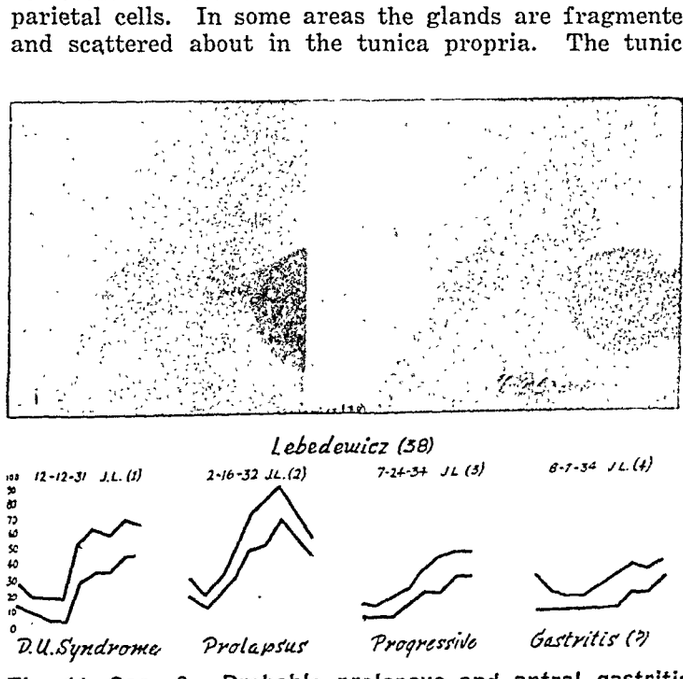


Fig. 11, Case 9. Probable prolapsus and antral gastritis with hyperacidity. Showing progressive diminution of acid in spite of "gastritis" therapy and ablation of dental foci.

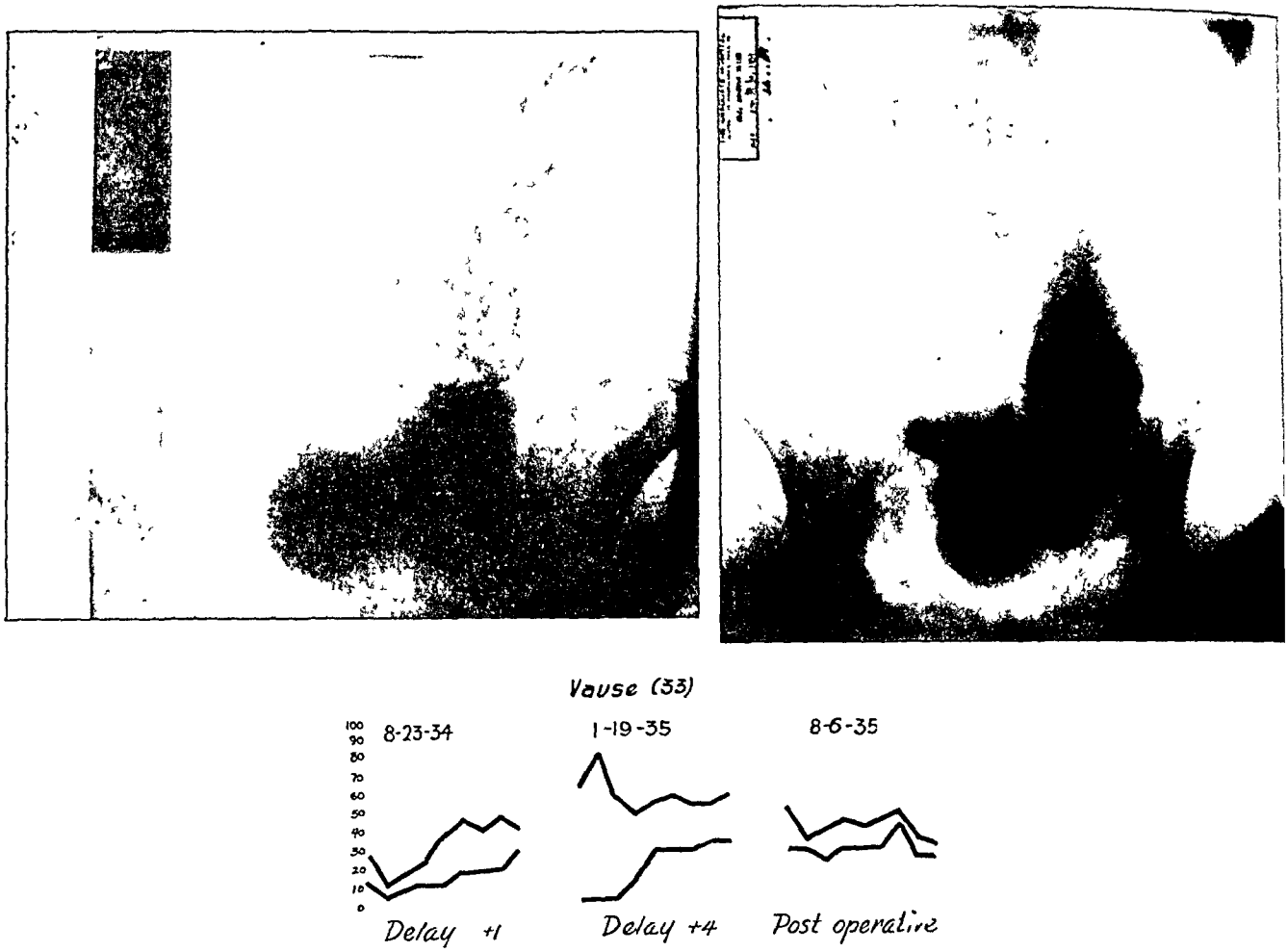


Fig. 12. Case 10. Progressive pyloric obstruction in association with hypochlorhydria due to pyloric ulcer or stenosing pyloric gastritis.

propria or corium of the mucosa is degenerated in places and the seat of old hemorrhages. In other places it is densely infiltrated with wandering cells, plasmacytes greatly predominating instead of the lymphocytes which are normally present in this fibroreticular tissue.

Comment: It is conceivable that the cardiospasm may have resulted from an infiltration of the nerve plexus in the terminal esophagus secondary to an esophagogastritis in much the same way which Hurst has accounted for some cases of "achalasia" of the cardia from infiltration of Auerbach's plexus in syphilis. The patient did not have tuberculosis or syphilis or any appreciable anemia. Two other cases of cardiospasm are being followed with clinical and laboratory evidences of gastritis.

DISCUSSION

The diagnosis of gastritis in this group, which share commonly an improvement in secretory status, is largely dependent upon examinations of the gastric residue and lavage fluid. We do not agree with Hurst that excessive mucus alone is pathognomonic of gastritis any more than we would designate all cases "colitis" because of mucus in the colon. Indeed caution is necessary in the interpretation of microscopic evidence of inflammation and desquamation in terms of gastritis unless the sediment is excessive and not due to oral or duodenal influx. X-ray evidence of gastritis was suggestive in cases 17, 22, 23, 6 and 14. Needless to say, many cases of proved gastritis may show little by ordinary X-ray examination.

These cases illustrate the various agents which may be responsible for improvement in the level of gastric acidity. Gastric lavage, two or three times weekly, was used in 4 cases. Sinus drainage and treatment were followed by a change from apparent achylia to normal acidity in one case. A cleaning-up of dental foci may have had a beneficial effect in one and tonsillectomy in another. In 2 cases improvement in the secretory status followed the administration of vitamine B. One was an alcoholic pellagrin. The other patient gradually showed a return to normal acidity from an apparent achylia while taking yeast and hydrochloric acid. This apparent response to vitamin B is of interest in view of the recent inability of Alvarez *et al* to reduce gastric acidity in normal people by deprivation of vitamin B_1 for six weeks. It would be interesting to repeat their experiments on patients with gastritis. It is possible that excessive amounts of vitamin B_1 are essential to the maintenance of acid in these cases. The improvement in secretion following splenectomy for Banti's disease in one patient and the probable benefit from antiluetic treatment in another is readily understood.

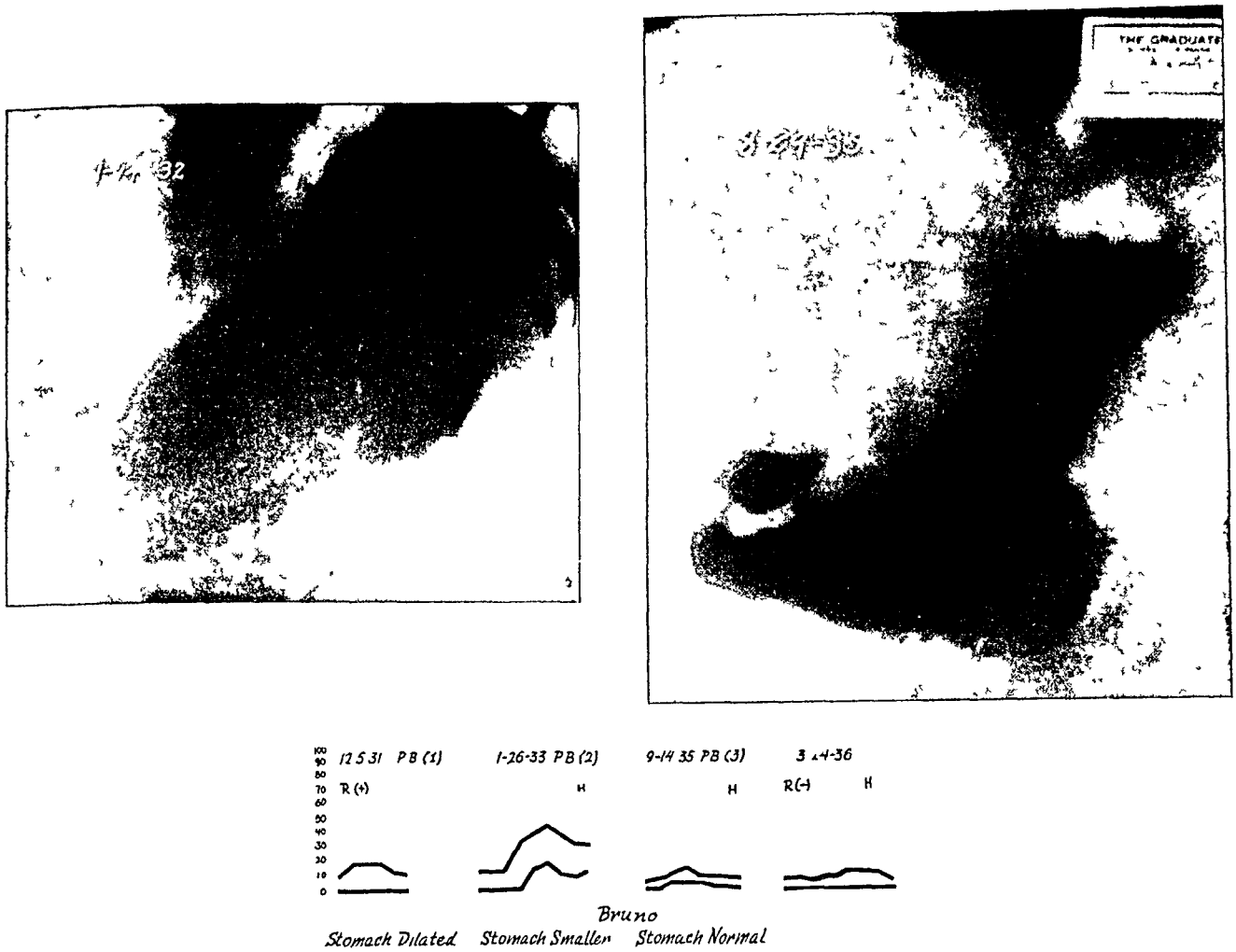


Fig. 13, Case 3. Dilated stomach with achlorhydria in man of 78, suspected of carcinoma in 1931. Showing gradual return of stomach to normal size and development of histamine refractory achylia during 4½ years.

The most significant finding in this group of patients is their youth. All were under thirty-five except the alcoholic pellagrin and the leutic patient. In 1932, we reported 65 cases of achlorhydria by the ordinary two-hour Rehfuss fractional gastric analysis, which were subsequently tested with histamine Only five of this group under age thirty showed achlorhydria after the ordinary analysis and only two of the five had a true achylia gastrica after histamine injection. Three cases in this present series with apparent achlorhydria were under age 26. None was proved to be truly achylic and all responded to treatment. This reflects our usual experience Absence of both acid and enzyme after histamine injection is exceedingly rare under age 30 and apparent achylics (without histamine) under age 30 usually show a secretory response to histamine and a clinical response to gastritis treatment. If a diathesis for achlorhydria exists, all evidence certainly indicates that it does not often become manifest until age forty or later. Experience with achlorhydria and hypochlorhydria in youth indicates that attention paid to the ablation of foci in the nose and throat and mouth, stomach rest, lavage, vitamine B, and attention to other etiological factors which may be responsible for gastritis, offers an excellent chance of improvement in the secretory status and clinical condition of the patient.

GROUP II—CASES OF POSSIBLE GASTRITIS WITH LOW OR DIMINISHING GASTRIC SECRETION

For purposes of comparison, it should be of interest to study a group of patients without true achylia, who failed to show improvement in gastric secretion on appropriate treatment.

Normal acid to hypochlorhydria. Case 13, S. M., an Italian male, 38 years of age, complained of early morning and early postprandial epigastric distress for two years. He gave a history of malaria in 1911 and of gross dietary indiscretions and showed marked dental sepsis. The fasting gastric contents suggested diffuse mucosal inflammation with microscopic food remnants, and the roentgen diagnosis was gastro-duodenitis. . Normal gastric acidity in December, 1932, was gradually replaced by an extreme hypochlorhydria during the next year (Fig. 10) in spite of symptomatic relief by occasional gastric lavage, smooth diet and hydrochloric acid.

Case 9, J. L , white male, 38 years of age, gave a history of nausea, vomiting and epigastric distress and possibly hematemesis at irregular intervals for 5 years. The past history revealed attacks of scarlet fever, influenza and quinsy Apical dental abscesses, pyorrhea and diseased tonsils were present. The gastric residua were suggestive of gastritis and slight delay in stomach emptying. X-ray pointed toward a prolapsus of the gastric mucosa through the pylorus A progressive depression of the secretion

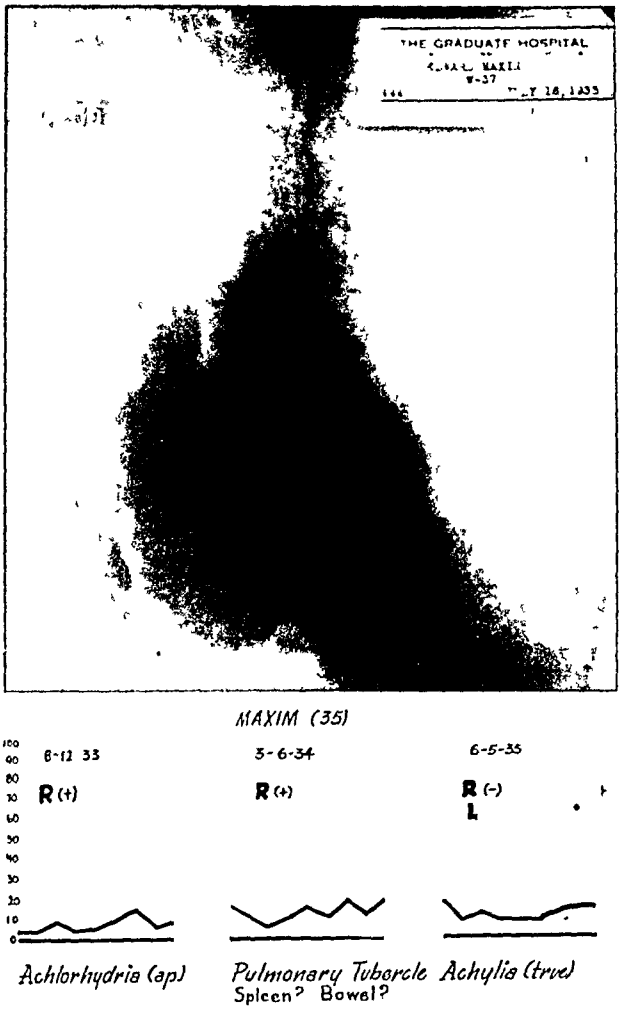


Fig. 14, Case 31. Pulmonary tuberculosis with X-ray evidence suggestive of gastritis with an apparent achlorhydria changing to histamine refractory achylia.

curve occurred between February, 1932, and August, 1934, (Fig. 11) in spite of a modified ulcer regimen and removal of dental foci.

Comment: These two cases have in common the factor of age, normal acidity on admission, slight delay in stomach emptying, excessive mucoid and cellular gastric sediment, the absence of a circumscribed gastric or duodenal lesion and symptomatic relief on a gastritis regimen. Both exhibited a striking and consistent trend downward to the point of definite hypochlorhydria

Gastrectasia with hypochlorhydria. Case 10, D. V., a colored female, 33 years of age, appeared in August, 1934,

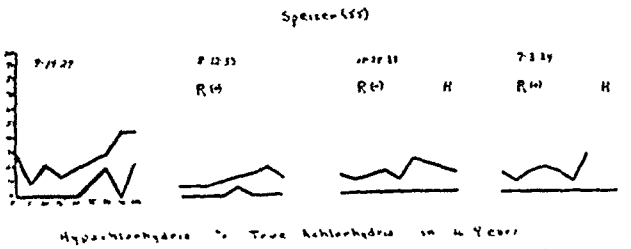


Fig. 15, Case 27. Hypochlorhydria to histamine refractory achylia in 4 years with return of enzyme after histamine 8 months later.

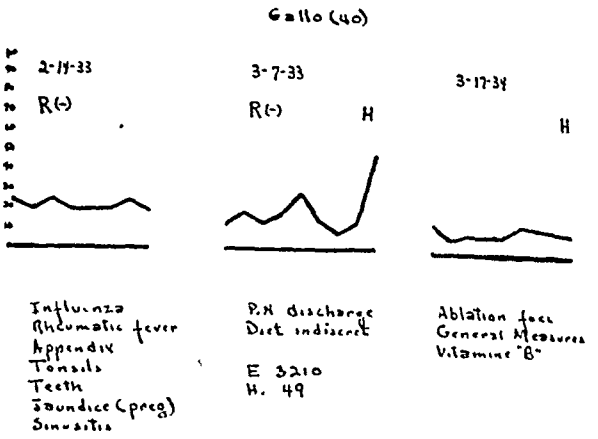


Fig. 16, Case 4. Hypochromic, microcytic anemia with gastritis and histamine refractory achylia showing the anticipated failure of secretory response to "gastritis" treatment.

complaining of abdominal pain, nausea and vomiting since June. Gastric extractions and X-ray studies suggested gastritis in a dilated retentive stomach without evidence of a circumscribed lesion. Gastric analysis showed a hypochlorhydria (Fig. 12). Possible causes for gastritis comprised scarlet fever, rheumatic fever, frequent attacks of tonsillitis, influenza and abscessed teeth. Hospitalization on an ulcer regimen improved stomach emptying and rendered her symptom-free. Symptoms recurred in December and became progressively those of pyloric obstruction, practically complete by X-ray in January 30, 1935. A gastroenterostomy was performed February 18, 1935. A stenotic pyloric ulcer was reported by the surgeon. Carcinoma of the stomach had been suspected.

Comment: It is of interest to speculate concerning the sequence of events. Those who favor a primary gastritis to account for hypochlorhydria and ulcer would undoubtedly point to the history of multiple streptococcal infections to support the contention of an antecedent pangastritis. Others might postulate that a constitutional hypo-acid diathesis accounted for the hypochlorhydria and rendered the stomach more susceptible to gastritis. A third possibility would grant a primary pyloric ulcer developing in an hypo-acid

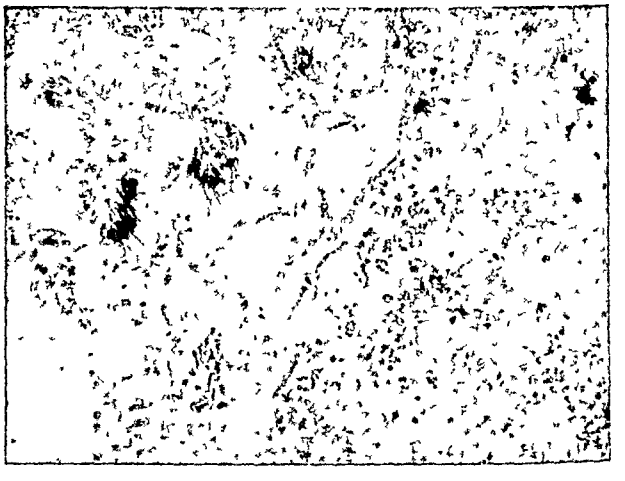


Fig. 17, Case 4. Moffitt preparation of gastric sediment aspirated through stomach tube, showing columnar epithelium in palisade arrangement in a field of mucus.

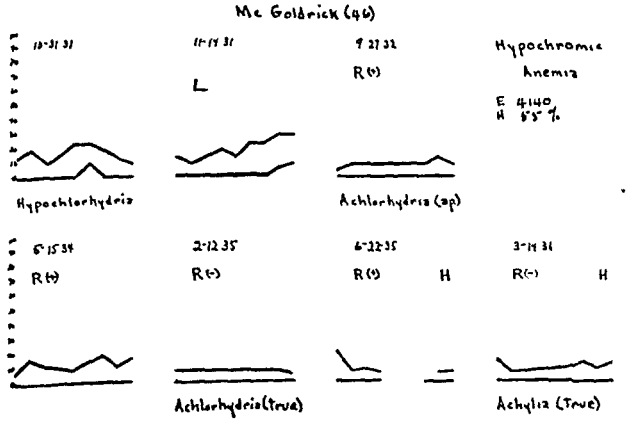


Fig. 18, Case 7. Enlarged stomach with hypochromic anemia gradually changing from an hypochlorhydria to an histamine refractory achylia in 4½ years.

stomach, the gastritis being dependent upon gastric stasis secondary to the ulcer. Somewhat against the latter argument is the rare association of juxtapyloric ulcer and hypochlorhydria. The case illustrates very well the difficulty of deciding between a primary gastritis (Faber), gastritis conditioned by a hypo-acid diathesis (Hurst), and gastritis secondary to gastric retention.

Case 8, P. B., male, 78 years old, was admitted in December, 1931, complaining of early postprandial epigastric distress for one year. Factors considered of etiological significance were frequent respiratory infections, a fondness for highly seasoned foods, diseased tonsils and arteriosclerosis. A provisional diagnosis of cancer near the pylorus was based upon his age, a short history, markedly enlarged stomach and an achlorhydria with highly cellular mucoid gastric residue. Operation was refused. The stomach decreased progressively in size and the patient improved symptomatically and in March, 1936, (4½ years later) was still carrying on. In January, 1933, he showed acid after histamine injection, which steadily diminished to a true achylia in March, 1936, (Fig. 13).

Comment: Another case of marked secretory deficiency in association with extreme enlargement of the stomach, differing from the preceding case in that gradual reduction in stomach size occurred with stomach rest. Comparable curves after histamine show progression downward to achylia from January, 1933, to March, 1936. Because of the absence of stomach symptoms until 77 years of age, it would appear that this belated achylia probably developed on the basis of an arteriosclerosis with secondary gastritis. It is conceivable that the tremendous dilatation on admission

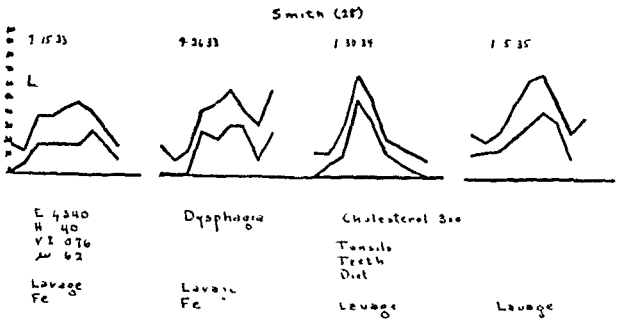


Fig. 19, Case 5. Typical hypochromic microcytic anemia changing from hypochlorhydria to normal acidity with "gastritis" treatment including lavage and tonsillectomy.

may have been due to a pyloric gastritis. Indeed both of these cases and Case 23 of the preceding group may represent examples of the stenosing type of gastritis described by Boas, Konjetzny and Faber.

True achlorhydria to true achylia. Case 31, E. M., Jewish male, 35 years of age with active pulmonary tuberculosis, slightly enlarged spleen and possibly early ileacecal tuberculosis, also had diseased tonsils and abscessed teeth. The gastric sediment suggested gastritis. The roentgen mucosal pattern in March, 1934, showed greater curvature markings which had increased in depth and irregularity in July, 1935. At this time the greater curvature showed definite speculization, a type of mucosal distortion, which we feel is most suggestive of gastritis. In August, 1933, a true achlorhydria was noted (rennet positive). Finally in March and in June, 1935, even rennet failed to appear after histamine injection—a true histamine refractory achylia (Fig. 14).

Case 27, N. S., a white male of 55 years, complained of vague distress, pyrosis and regurgitation soon after meals for three years. Oral sepsis was marked. He showed excessive quantities of fasting gastric mucoid and cellular sediment. He responded slowly to a gastritis regimen but showed a trend downward in gastric secretion from hypochlorhydria (Sept., 1929) to true achylia in November, 1933. In July, 1934, rennet reappeared after histamine (Fig. 15).

DISCUSSION, GROUP II

This group as well as the preceding one illustrates nicely the mechanism of changing gastric secretion. The trend downward is almost always gradual. In this group the secretory status diminished often in spite of clinical improvement and the recovery of gastric tonus. The first two cases (13 and 9) started from normal and receded to hyponormal in one and three years. Three cases illustrate the final stage of development of true achylia (3, 21, 27). The two older patients (56 and 78 years) slowly progressed to achylia in spite of clinical improvement. Proof is again presented to support the primary disappearance of acid with a persistence of enzyme secretion for some time afterwards. Improvement rarely occurs after the development of histamine refractory achylia. If it does, the secretion of enzyme without acid may occur, as in Case 27. The time required for the development of a true achylia is worthy of emphasis—4½ years were required from extreme hypochlorhydria to true achylia in Cases 3 and 27. The gradual depression of secretion over a period of years favors the conditioning influence of gastritis.

The age of the patient seems to be an important factor. Four of 5 patients with diminishing secretion were over 38 years of age. The other was only 35 years old but had advanced tuberculosis. After age 40 or thereabouts secretory response to treatment is less apt to occur. Whether this is due to the progression of the gastritis, decreasing blood supply, or a middle-aged hypo-acid diathesis, as suggested by the hypo-acid trend in anemic families, remains to be shown.

Lavage preceding gastric analysis has not proved as successful in immediately raising the acid level as Hurst reports—here again the age factor is significant. The degree of response both to histamine and lavage seems to diminish with age. It is noteworthy in the entire group of cases that acid response to histamine in the apparent achlorhydrias may be delayed—often until the second hour. This is mentioned because in

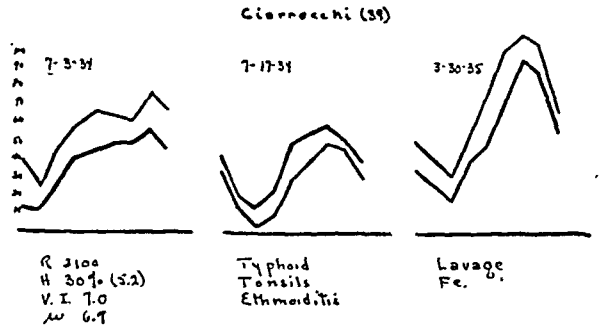


Fig. 20, Case 8. Hypochromic, microcytic anemia changing from normal to extreme hyperchlorhydria following "gastritis" management with lavage.

normal stomachs the maximum increase occurs from 15 to 30 minutes after injection. Obviously a diagnosis of histamine, refractory achylia cannot be made in cases of gastritis unless the test is continued for the full two-hour period.

Several of these cases emphasize the necessity for paying more attention to gastric retention as a possible cause for the gastritis—a factor which may account for the high incidence of gastritis in association with ulcer. Cases 13 and 9 tend to support Hurst's contention that antral gastritis is not necessarily associated with hyperacidity.

GROUP III—HYPOCHROMIC, MICROCYTIC ANEMIA

In 1909, Faber described "simple microcytic anacid" anemia and in 1913 he mentioned a typical case of this disease, which showed a characteristic follicular gastritis at necropsy. He has recently expressed the opinion that the gastritis causing the anacidity may in some way account for this type of anemia which usually responds to iron. Achlorhydria seems to be accepted as a necessary concomitant in the diagnosis of this type of anemia in many quarters. A group of cases are briefly reviewed in order to illustrate the behavior of the gastric acidity.

Case 4, M. G., a white Italian multipera, 40 years of age, complained of early postprandial epigastric distress and weakness. Factors held responsible for the gastritis were influenza, overindulgence in coarse, highly seasoned foods and coffee, frequent attacks of tonsillitis, multiple dental foci, chronic pansinusitis, nasal polyps, chronic postnasal discharge, and jaundice with a recent pregnancy. Repeated gastric lavage exhibited gastritic sediment. Tissue sections prepared from the sediment showed excessive desquamation of surface epithelium and deeper glandular elements (Fig. 17). X-ray of the stomach was essentially negative. In February, 1933, the erythrocytes were 3,210,000 and the hemoglobin 49 per cent. Frequent gastric analysis showed a true achylia gastrica which persisted in spite of therapy directed toward a possible gastritis (see Fig. 16).

Case 7, M. Mc., a white female, appeared in October, 1931, at the age of 46, complaining of alternating diarrhea and constipation, anorexia, morning nausea and retching. No etiologic factors for gastritis were elicited except for marked dental sepsis for which treatment was refused. X-ray showed a markedly dilated stomach with greater curvature serrations and irregularity. The gastric sediment was suggestive of gastritis. In June, 1934, the erythrocytes were 4,140,000 and the hemoglobin 55 per cent. X-ray at this time showed marked reduction in stomach size.

Comment: The case demonstrates a gradual reduction in gastric secretion from a marked hypochlorhydria in 1931 to a histamine refractory achlorhydria in June, 1935, and finally a true achylia in March, 1936, (Fig. 18).

Case 5, G. S., a colored female, 28 years of age, free from gastro-intestinal complaints, was first seen in July, 1933. She gave a history of excessive indulgence in hot and highly seasoned foods, and had infected tonsils and dental caries. The blood count showed 4,340,000 erythrocytes, 40 per cent (7.0 gm.) hemoglobin, 5,300 leukocytes, a volume index of 0.76 and an average red-cell diameter of 6.2 microns. The blood cholesterol was 300 milligrams and the basal metabolic rate minus 3. The gastric sediment was suggestive of gastritis. The X-ray was essentially negative. The special tissue preparation of the gastric sediment was of no significance. Recurring bouts of dysphagia developed soon after treatment was started.

Comment: Startling with a marked hypochlorhydria the secretory trend was definitely upward. This may have been due to stomach rest, therapeutic gastric *lavage or removal of diseased tonsils (Feb., 1935)*. The anemia responded satisfactorily to iron (Fig. 19).

Case 8, M. C., an Italian female, 39 years of age, was first studied in July, 1934, giving a history of typhoid fever, frequent sore throats, chronic ethmoiditis, long-standing constipation, and having grossly diseased tonsils. The blood-count showed 3,100,000 red-cells, 30 per cent or 5.2 grams of hemoglobin, reticulocytes 0.5, volume index 0.7, average size of red-cells 6.7 microns. Lavage caused the recovery of excessive gastritic sediment. The stomach films were negative except for a serration of the proximal half of the greater curvature. A normal acidity was present in July, 1934. The patient was given therapeutic lavage at frequent intervals, put on a smooth diet, the bowels were regulated and iron therapy started. In March, 1935, the acidity curve was that of a grade 3 hyperacidity (Fig. 20).

Comment: The case illustrates the occurrence of a typical hypochromic microcytic anemia with a normal gastric acidity changing to a high-grade hyperacidity after the institution of therapy directed toward a possible gastritis and treatment of the anemia with iron.

Case F., M. G., a colored female, age 31 years, was first seen in January, 1933. She was free from gastro-intestinal complaints and was being followed in the medical clinic for symptoms attributable to anemia. The red-cells were 4,830,000, hemoglobin 55 per cent, or 9.5 grams, leukocytes 4,000, reticulocytes 0.3 per cent, volume index 0.75 per cent, Wassermann positive. The stomach acidity was normal and the fasting and lavage sediment suggested gastritis. The Moffitt preparation of the sediment showed neutrophils, degenerated cells from the gastric mucosa and nuclear remnants. The anemia responded to iron. In April, 1935, she was placed on therapeutic lavage and the tonsils were removed. In February, 1936, re-ray indicated a slight tendency toward irregularity of the greater curva-

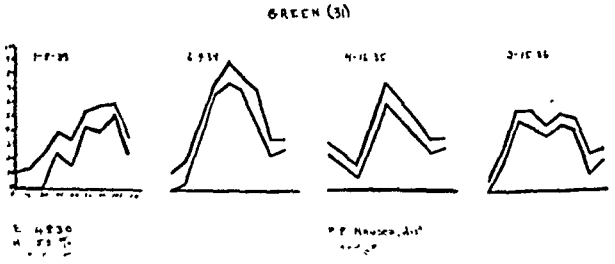


Fig. 21, Case "F." Hypochromic microcytic anemia with normal acidity and hyperacidity.

ture of the stomach, suggestive of gastritis. The gastric acidity curve mounted in June, 1934, then returned to normal (Fig. 21).

DISCUSSION, GROUP III

Five female patients with hypochromic microcytic anemia are presented in order to emphasize the frequent occurrence of all varieties of gastric secretory behavior in this type of anemia. The three younger patients had normal acidity. Three other patients have been followed with typical hypochromic microcytic anemia, originally having a normal acidity, who subsequently became achlorhydric. They were not included in this group because special examinations for gastritis were not performed. Cases 5 and 8 show that actual improvement in the acidity level may follow treatment in the younger age group. Case 5 with an extreme microcytosis started with a definite subnormal acidity and later had normal secretion. The status of this case is further fortified by the development of dysphagia, simulating a Plummer-Vinson syndrome without achlorhydria. The two older patients, Cases 4 and 7, showed a low secretory level, one gradually developing a true achlorhydria after 4 years and the other showing a true achylia from the start. The secretory behavior in these cases does not support the pathogenetic importance of a primary achlorhydria in hypochromic, microcytic anemia.

The cases were segregated from material considered clinically to have gastritis, although the proof of the gastritis was not always irrefutable. All had an excessive amount of gastric sediment in the fasting residuum and after astringent lavage. Roentgen evidence was not striking but was suggested in Cases 8, 7 and F. Histologic study of sections prepared from the gastric sediment suggested excessive desquamation and degeneration of gastric mucosa in Cases 4 and F. The elevation in gastric acidity in Cases 5 and 8 would be considered by Hurst and Faber as evidence strongly suggestive of an underlying gastritis. The very gradual depression in acidity over a four-year period in Case 7 corresponds to the manner of development of achlorhydria in gastritis described by Faber.

The group analysis suggests a common factor of gastritis and supports, in some measure, the contention of Faber that the anemia results from a primary gastro-duodenitis interfering with the elaboration of a specific antianemic factor. This mechanism would explain the frequent absence of achlorhydria until the gastritis has become general or until the gastritis has decreased the utilization of vitamine B, sufficiently to interfere with normal-acid secretion. The "gastritis" theory does not sufficiently explain the sex peculiarity of the anemia and our cases strongly suggest a concomitant thyroid-ovarian dysfunction, which must be woven into the pattern of hypochromic, microcytic anemia before it is complete. Nevertheless, we feel that complete therapy must include attention to the gastritis which is probably almost always present. There is nothing in the study of these cases which refutes the existence of an underlying familial or constitutional diathesis accounting for an increased susceptibility to either gastritis or anemia or both. Indeed, this may constitute the connection with the endocrine system and account for the difference in secretory behavior which seems somewhat related to the age of the patients.

SUMMARY

The gastric secretory behavior of a group of cases with suggestive clinical evidence of gastritis has been studied for periods varying from 3 months to 6 years. Gastritis in association with ulcer and cancer and with primary hyperacidity are not included.

For purpose of analysis these cases were divided into 3 groups: (1) those with absent or reduced acidity, showing improvement in the secretory status following treatment; (2) those with low sustained or diminished levels of gastric secretion and (3) a group having in common a hypochromic microcytic anemia.

Therapeutic measures of possible significance in improving the secretory status are discussed and illustrated. Marked improvement in the level of secretion may occur in any patient who does not show a true histamine refractory achylia, but the chances of a sustained elevation in secretory status diminishes with the degree of secretory suppression originally encountered. Clinical improvement usually parallels increased secretion in the hypo-acid group but may occur in many cases in which no elevation in the secretion curve takes place.

The most important factor influencing the secretory response to therapy is that of age. States of reduced secretion, except true achylia, occurring in patients under 35 years of age frequently show improvement. After the age of 40, such improvement is less commonly encountered. The amplitude of the immediate secretory excursion after histamine injection or gastric lavage in hyposecretion states is likewise diminished after age 40. If a hypochlorhydric or achlorhydric diathesis exists, it must remain latent in most instances until middle life. The relative significance of gastritis and of a so-called hypo-acid diathesis in achlorhydria is discussed.

The trend upward in acidity in hypochlorhydria or achlorhydria may occur very rapidly, but the trend downward is usually very slow and methodical. Evidence is presented to indicate that true achylia may not occur until many years after the acidity has started to fall. The secretion of gastric enzymes practically always persists for a time after acid secretion has ceased.

The response to histamine injection may be delayed much beyond 30 minutes in cases of chronic gastritis with apparent achlorhydria.

Three cases are included with extreme gastrectasia and hypochlorhydria, which may have depended upon a stenosing type of gastritis as described by Faber, Konjetzny and Boas.

Evidence is presented which suggests that hypochromic, microcytic anemia which responds to iron therapy may be conditioned primarily by gastritis. The anemia is often found in the absence of achlorhydria. The significance of gastritis in this type of anemia is discussed.

DISCUSSION

DR. BURRIL B. CROHN (New York City): Dr. Bockus' modest last statement really constitutes my discussion. I feel like the witness who is before the Congressional Committee and to inquiries says that either he forgets or he doesn't know. When it comes to talking about gastritis I feel the same way. I do not know what gastritis is. I do not think that anybody can definitely say

what constitutes gastritis either pathologically, clinically, from the standpoint of secretory changes, and certainly not from the clinical behavior of the patient. Certainly the clinical diagnosis of the gastritis is just about the most dangerous ground to step on that I can possibly imagine.

I am glad to see Dr. Bockus take up the study of gastritis. I believe that Dr. Bockus described in previous years the secretory changes of an anacid nature taking place with advancing years. The acid curve is at its maximum about the age of 20; the incidence of anacidity gradually progresses and reaches a maximum at the age of 55. I wonder whether Dr. Bockus is implying now that that gradual diminution of acidity is based upon actual pathological changes in the mucosa of the stomach wall, in the nature of gastritis.

I wonder if any two or three pathologists sitting down to the microscope with the same slides would agree to what constitutes gastritis, whether the small increase of round cells, plasma cells and leucocytes constitutes a disease; and, if the increase of cells is a disease, whether that disease is capable of diagnosis as gastritis?

Missing from Dr. Bockus' paper are the gastroscopic pictures. If we are to depend at all on the diagnosis of gastritis one would want gastroscopic confirmation and would want more histological findings to parallel these changes.

In the old days we recognized gross variations in gastric secretion. We spoke a great deal at length about the variations in gastric secretory curves in the same individuals under varying conditions and we recognized that there was no such thing, even in the same individual, as an identical curve under all conditions.

I just wonder if Dr. Bockus in showing these various curves during states of debility, for instance, in contrast to states of increased health, whether these variations and fluctuations in acidity aren't greatly dependent upon functional and secretory changes rather than on actual organic changes in the mucous membrane?

DR. H. L. BOCKUS (closing the discussion): I should like to take this opportunity to apologize to Dr. Crohn for not having given him the paper previous to the meeting. Unfortunately the illustrations were not completed in time.

There are several points mentioned by Dr. Crohn that I shall try to elaborate on a little. First of all the diminution in the levels of stomach acid. That is open to a number of interpretations, as Dr. Crohn well knows. If you talk to Dr. Knud Faber, he will tell you that this is definitely indicative of and dependent upon gastritis. Dr. Hurst on the other hand feels that the gradual diminution in acid results from gastritis conditioned by an hypoacid diathesis. We were able to confirm Dr. Hurst's contention that he has never seen a hyperacidity in diffuse gastritis gradually give way to a true achylia. We have looked carefully for a case of that type and, to our surprise, so far we have not found one.

As far as gastroscopy is concerned, most of these patients were examined through the gastroscope. I do not feel so confident as Dr. Crohn apparently does that one can make invariably a definite diagnosis of gastritis by gastroscopy. We have looked at over 150 stomachs in that way, and I feel that there is a great need for further study and classification before one's experience justifies a diagnosis of gastritis based entirely upon the gastroscope.

We have had a conservative roentgenologist collaborating with us and we are not prepared at this time to say anything about the roentgenologic findings. In some instances the roentgen findings have been characteristic, but one should not expect to find X-ray evidences of gastritis in every case, and naturally the mucosal pattern differs greatly in gastritis.

I reiterate my previous statement that we have no absolute diagnostic criteria for the diagnosis of this type of gastritis, either through the gastroscope or the X-ray or the examination of the gastric sediment. All three methods should be utilized. We should like to see enough interest stimulated so that all of these methods will be used in various places, hoping that at some later date an established criterion for the diagnosis of gastritis of various types will emerge.

Dr. Crohn mentioned the slight changes in our acid curves. The changes were not slight. They were great, particularly in the younger patients whose acid levels mounted. The upward trend in some instances was phenomenal. The mechanism of changes in gastric acidity of the type mentioned is not always clear. It may depend upon removal of a mechanical impediment to the flow of juice, such as mucus in the gastric tubules, or rapid diminution in the size of swollen cells, or it may be due to improvement in a deficiency state which has conditioned the hypoacidity or anacidity, or upon other factors little understood.

Intracutaneous Responses, Comparable to Positive Frei Reactions, with Colonic Exudate from Chronic Ulcerative Colitis Cases with Positive Frei Tests*

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THERE was reason to believe that among cases classed as idiopathic ulcerative colitis, with and without stricture, some might be due to a virus or viruses, probably to the virus of lymphogranuloma inguinale. If proved, a virus as a cause of intestinal disease would come into being, and the idiopathic ulcerative colitis group would be further narrowed. In this connection, it was recognized that a positive Frei test indicating the past or present presence of lymphogranuloma inguinale in a patient with an otherwise unexplained ulcerative colitis did not of itself prove that the causative L.i. virus was etiologically related to the colitis. It was conceivable, in some instances at least, that the colitis might not bear any relation to an antecedant, simple, uncomplicated and healed infection, as reminded by the positive Frei intradermal reaction. Also, it was recognized that the mere presence of a virus was neither proof of the presence of disease nor responsible for the disease with which it appeared to be associated. However, the first step in attempting to demonstrate colitides of possible virus origin, rested in the isolation or indication of the presence of such an agent directly from the suspected colonic involvement. It is with these attempts that this communication is concerned.

It was hypothesized that if antigens could be prepared from bowel material of those with ulcerative colitis having a positive Frei test, which would give comparable reactions with the Frei antigen, and if the test antigen responses could not be ascribed to foreign protein, to a known bacterium or toxin, that such results consistently secured might indicate the probable presence of a virus or viruses in such intestinal exudate.

PROCEDURES

I. Sources:

(A) Cases presenting a positive Frei test with an otherwise unexplained ulcerative colitis with and without stricture but without elephantiasis or vegetations.

(B) Cases presenting a negative Frei test with an unexplained ulcerative colitis.

(C) Cases presenting a negative Frei test without colitis.

II. Methods:

Since it was desirable here to work with bowel material free from bacteria, and since the virus of L.i. is considered by some to be filterable, filtration experiments were done as follows:

(A) Preparation of Antigen. A few hours following saline enemas, patients were rectosigmoidoscoped and about 1 to 5 c.c. of grossly fecal-free material usually of a muco-purulent nature with or without gross blood, were aspirated into a large tube containing glass beads and 5 c.c. infusion bouillon. Sterile technique was employed throughout. This material was then well shaken and bouillon dilutions of 1:5 or 1:10 were made. This was filtered through sterile non-absorbent cotton to remove larger particles which interfere with filtration, and then passed through Seitz and Berkfeld V or N filters.* The bowel filtrate was then heated at 60° C. for two hours and on the following day for one hour.

Aerobic and anaerobic sterility tests were done immediately after passage through the filter, after heating, and after the addition of 0.25% phenol for preservative purposes.

(B) These antigens were then inoculated intradermally in the same amount as is the Frei antigen: 0.1 c.c. The results were read at 48 hours and 9 days; in many instances readings were made at later dates. Intradermal inoculations usually with more than one known active Frei antigen were done simultaneously for comparative purposes.

RESULTS

1. *Two Seitz-filtered bowel antigens* from two ulcerative colitis cases with positive Frei tests, one with and one without stricture, were tested on seven cases exhibiting positive Frei reactions. All were unquestionably negative. In no instance did the reaction attain a size of more than 2 mm., and that only once.

2. *Nine Berkfeld-filtered bowel antigens* from five ulcerative colitis cases with positive intradermal Frei reactions and from four such cases with negative Frei responses, were tested upon six cases exhibiting positive and five negative Frei tests. One of the positive Frei cases gave intradermal indurations in excess of 5 mm., with two antigens from ulcerative colitis cases evidencing positive Frei tests, at 48 hours. One week later—nine days after inoculation—these reactions had disappeared. This was not regarded as of significance in view of the fact that all of the remaining cases

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*The filters were tested by means of air pressure for gross leaks as well as their ability to retain B. prodigiosus and B. pyocyaneus, prior to use on each occasion.

CHART I

Intradermal responses of those with ulcerative colitis and positive Frei reactions to an antigen of unfiltered bowel exudate from an ulcerative colitis-positive Frei case

"McK" Antigen						
	1:15			1:30		
Case	48 hrs.	9 days	14 days	48 hrs.	9 days	14 days
No. 1 L.B.	± 6x5	+ 8x6	X	X	X	X
No. 2 M.A.	— 4x4	+ 4.5x5	— 3x4	— 3x3	— 3x4	+ 4x5
No. 3 S.S.	± 5x3	+ 6x5	X	X	X	X
No. 4 S.McK.	X	X	X	X	X	X
No. 5 E.B.	± 5x3	+ 7x4	X	— 3x3	+ 5x4	X
No. 6 V.S.	— 4x4	+ 5x4	+ 5x4	— 3x4	— 3x3	—

X — Never done.

were definitely negative and the reaction did not persist for at least 9 days.

In view of the apparent inability to demonstrate the presence of any reaction-producing substance in filtered bowel exudate by this method, attempts were then made to prepare antigens of unfiltered material. It was collected in the manner already described and diluted 1:5 with saline. This was then heated in sterile vials at 60° C. for two hours, and for one hour on the following day. Aerobic and anaerobic sterility tests were made after heating and again after the addition of 0.25% phenol for preservative purposes. Dilutions were prepared as further indicated in the Charts. 0.1 c.c. was inoculated intradermally and the readings were obtained usually at 48 hours, at 9 days, and in many instances later. Twenty-four attempts to secure material from nine cases of ulcerative colitis evidencing positive Frei tests resulted in the obtaining of three antigens. Two of these ("J" and "McK" antigens) were free of viable bacteria. In one ("O.L.") an alpha-zoned (green producing) enterococcus persisted. This antigen was used despite the presence of the organism, for reasons to be discussed later. In the remainder, more than one type of organism survived. This also occurred in each of eight attempts from five ulcerative colitis cases with negative Frei reactions. Such material was discarded.

Intradermal inoculations with known active Frei antigens were done simultaneously for comparative purposes. Intradermal reactions for chancroids in the human sources of the three test antigens employed were negative. Intestinal tuberculosis was eliminated.

RESULTS

The three antigens were tested on six ulcerative colitis cases with positive Frei reactions. The controls consisted of thirteen cases presenting negative Frei responses; three were diagnosed as ulcerative colitis, two as chronic indeterminate diarrhea, and eight as functional dyspepsia.

Criteria used in determinations: The preparation of the antigens from unfiltered bowel material, the

CHART II

Intradermal responses of those with ulcerative colitis and positive Frei reactions to an antigen of unfiltered bowel exudate from an ulcerative colitis-positive Frei case

"J" Antigen									
	1:12			1:24			1:48		
Case	48 hrs.	9 days	14 days	48 hrs.	9 days	14 days	48 hrs.	9 days	14 days
No. 1 L.B.	— 4x4	— 4x3	X	X	X	X	X	X	X
No. 2 M.A.	— 3x3	± 5x5	+ 5x4	— 3x3	± 5x5	+ 5x5	± 6x6	— 1x1	—
No. 3 S.S.	± 5x3	± 6x4	X	X	X	X	X	X	X
No. 4 S.McK.	— 4x4	± 1 cm.x8	+ 5x5	— 2x3	± 1 cm.x7	± 5x4	— 2x2	+ 1 cm.x1 cm.	+ 5x5
No. 5 E.B.	— 4x3	— 6x5	X	— 3x3	— 4x3	X	— 2x2	— 3x4	X
No. 6 V.S.	— 4x3	— 3x4	— 4x4	— 3x2	— 3x4	— 2x2	— 2x2	— 4x4	— 4.5x3

X — Never done.

CHART III

Intradermal responses of those with ulcerative colitis and positive Frei reactions to an antigen of unfiltered bowel exudate from an ulcerative colitis-positive Frei case

	"O.L." Antigen								
	1:10			1:20			1:40		
Case	48 hrs.	9 days	14 days	48 hrs.	9 days	14 days	48 hrs.	9 days	14 days
No. 1 L.B.	+ 6x4	+ 5x4	X	X	X	X	X	X	X
No. 2 M.A.	+ 6x5	+ 6x5	+ 6x5	—	? 4x5 ?	+ 5x6	— 3.5x3	— 3.5x4	+ ? 4.5 (P) 4x4.5 (K)
No. 3 S.S.	— 4x3	— 5x5	X	X	X	X	X	X	X
No. 4 McK.	— 4.5x4	— 1.1 cm.x8	+ 5x4	— 4x4	+ 1 cm.x7	+ 5x6	— 3x2	+ 1 cm.x1 cm.	+ 8x6
No. 5 E.B.	+ 5x5	— 5x5	X	— 3x2	— 4x4	X	— 3x2	— 4x3	X
No. 6 V.S.	X	X	X	X	X	X	X	X	X

X — Never done.

method and amount of inoculation—as already noted—and the interpretation of the results were identical with that employed in the Frei technique. These criteria are those expressed by Wassen (1) with respect to the Frei reactions:

"The reaction is not read off until after 48 hours and a reddened and infiltrated dome-shaped papule is considered positive only if its diameter is at least 5 mm. . . . A positive reaction remains for a rather long time, as much as 8 to 12 days, as opposed to a non-specific reaction which is frequently very acute but also very transient."

It is to be added that the papule may go on to necrosis, that induration may on occasion be found to be more prominent that actual papule formation. The erythema extending beyond or that which is not associated with the papule or induration is not considered in the measurements.

SUMMARY OF TABULATED DATA

1. On the basis of the criteria just outlined, a perusal of Charts I, II and III indicates that all six cases of ulcerative colitis with positive Frei tests gave positive responses at 9 days after inoculation with one or more bowel exudate antigens. Of these, three cases (No. 2, No. 3 and No. 5) were positive with all three antigens, case No. 4 tested with two antigens was positive with both, case No. 1 was positive with two of three antigens, and case No. 6 with one of two antigens. Cases No. 2, No. 4 and No. 6, which reappeared for observation at 14 days, were still positive: case No. 2 was positive with two of three antigens, case No. 4 with two of two; and case No. 6 with one of two.

2. Of the thirteen negative Frei control cases submitted to bowel exudate antigens (Charts IV, V, VI), no definite positive intradermal reactions were obtained in any by the criteria outlined. Eight (cases No. 4, No. 5, No. 6, No. 7, No. 9, No. 11, No. 12 and No. 13) were negative with all three antigens; three (cases No. 1, No. 2 and No. 3) tested with two antigens were negative with both. Of the two remaining cases (No. 8 and No. 10) inoculated with three antigens, each presented one doubtful reaction: case No. 8 with the "O.L." antigen was positive at five days but negative at 12 days; case No. 10 with "McK" 1:15 antigen was not positive at 9 days but was at 16 days; they were negative with the other two antigens used.

3. Of the six ulcerative colitis cases presenting positive Frei responses, all revealed persisting reactions in excess of 5 mm. to the known active Frei antigens used at the end of 9 days. In the three cases observed on the 14th day, they were still positive.

DISCUSSION AND INTERPRETATIONS

The inability to demonstrate a substance indicative of a virus or some other significant agent in the filtered bowel exudate of those in whom such presence is suspected with this method, is in line with two unsuccessful attempts to obtain positive intracutaneous responses from Berkfeld (V and N) filtered bubo pus known to give positive Frei reactions when unfiltered. From a few such experiments with the virus of lymphogranuloma inguinale, Wassen (2) considers it is filterable. It has been passed through Chamberlain L1, L2, L3, and Berkfeld filters. However, this appears to have occurred irregularly, inconstantly. The Chamberlain type of filters referred to above are quite coarse allowing bacteria to pass, and hence were inapplicable to this work. The possible reasons for the negative results here with Berkfeld and Seitz filters were the slight concentration and virulence of the possible virus or its absorption by the filters.

It is believed that the constant and striking intracutaneous responses in those with ulcerative colitis and positive Frei tests and the negative intradermal reactions in those with negative Frei tests (controls), with antigens prepared, in consequence of filtration obstacles, from unfiltered bowel exudates of those with ulcerative colitis and positive Frei tests, are indicative of the presence of a specific substance or substances, probably of a virus nature. It seems likely that of the possible viruses, that of lymphogranuloma inguinale is present.

These skin responses to antigens of unfiltered bowel exudate are not purely of a bacterial nature. The cases from which the materials were secured for the preparation of these antigens were found negative for the Ducrey bacillus infection by means of the specific intradermal test for chancroid. The gonococcus, another possible cause, and syphilis, which rarely is re-

CHART IV

Intradermal responses of those with and without ulcerative colitis with negative Frei tests to an antigen of unfiltered bowel exudate from an ulcerative colitis-positive Frei case

Controls "McK" Antigen						
	1:15			1:30		
Case	48 hrs.	9 days	14 days	48 hrs.	9 days	14 days
No. 1 T.L.	X	X	X	X	X	X
No. 2 L.M.	X	X	X	X	X	X
No. 3 McC.	X	X	X	X	X	X
No. 4 F.T.	— 3x2	— 4x3	— 3x2	X	X	X
No. 5 F.E.	— 4x3	— 3x3	— 2x2	X	X	X
No 6 L.O.	— 3x3	— 3.5x4	X	— 1x1	— 2x2	X
No 7 D.	— 2x2	— 4x3	X	—	— 3x3	X
No. 8 F.O.	— 4x4	— 2.5x2.5	X	— 2x2	—	X
No. 9 L.E.	— 3x2	—	—	—	—	—
No. 10 M.M.	— 3x3	— 3x3	+ 5x5 *	— 1x1	— 2x2	— 3x3
No 11 M.	— 4x4	— 3x3	— 2x2	—	— 2x2	— 2x2
No. 12 S.	X	— 4x3	X	X	— 3.5x3	X
No. 13 V.	— 2x2	— 2x2	—	—	—	—

X — Never done.
* — Read at 16 days.

sponsible for conditions not unlike these studied here, give no specific reactions by a method such as this. Tubercle bacilli would not seem to be etiologic agents in these cases since such distal colonic involvement is usually a terminal stage of pulmonary tuberculosis and none here was tuberculous. Besides, the tuberculin test when positive persists usually for no more than 3 to 4 days. In this connection, it should be added that one of the antigens, "O.L.", despite the presence of a living alpha-zoned (green producing) gram positive enterococcus, and which was used only because of difficulties encountered in preparing an adequate number of unfiltered bowel antigens, gave the typically positive and negative responses in the positive and negative cases paralleling the reactions from both the test antigens containing no viable bacteria and the known active Frei antigens.

The responses with unfiltered bowel exudate antigens do not seem to be due solely to foreign protein or to toxins. Such reactions are relatively acute and transient. In the ulcerative colitis cases with positive Frei tests, the intracutaneous responses of 5 mm. or more persisted with undiminished size for at least 9 days and in nearly all cases for two weeks. In the negative Frei test (control) cases, the reactions were always under 5 mm. and did not manifest the same tendency to persist.

Thus, these skin responses cannot be considered either as a specific reaction to a known bacterium, toxin or as a result of foreign protein. These cutaneous allergic responses paralleling those produced by active Frei antigens are believed to be indicative of the presence of an inciting agent, unlike any of the above, possibly that of a virus. The recent research of Levaditi and his co-workers (3) appearing in April, 1935, while this work was in progress, is in line with this viewpoint.

The fact that the skin reactions with unfiltered bowel exudate antigens parallel known active Frei antigens does not of itself prove that the reaction is due to the inactivated virus of lymphogranuloma inguinale. It is possible that this may represent the presence of more than one virus. It is also possible that a distinctly different virus may give a reaction indistinguishable from that of Frei. Frei and Koppel (4) attempted to show the relationship between inguinal adenitis due to the virus of L.i. and genital and ano-rectal lesions by histopathologic methods. Frei later indicated (5) that this proof was incomplete. However, the experimental work of Levaditi and his co-workers referred to above indicates the unity of the etiology of lymphogranuloma inguinale and some cases of ulcerative colitis with positive Frei tests. Levaditi, in confirmation of the earlier hypothesis of Ravaut and his co-workers (6), reproduced the disease of lymphogranuloma inguinale in two with general paresis. The original source of the infective material was a biopsy specimen of an ano-rectal lesion from one with a positive Frei test. The patients prior to the inoculation presented negative intracutaneous reactions with Frei antigens and the antigen from the test material. After the establishment of the disease, the responses to these antigens were positive.

Attention is directed to the fact that the material employed by us and believed to contain the inciting agent, probably a virus, was a muco-purulent, some-

CHART V

Intradermal responses of those with and without ulcerative colitis with negative Frei tests to an antigen of unfiltered bowel exudate from an ulcerative colitis-positive Frei case

	Controls "J" Antigen								
	1:12			1:24			1:48		
Case	48 hrs.	9 days	14 days	48 hrs.	9 days	14 days	48 hrs.	9 days	14 days
No. 1 T.L.	—	— 3x2	— 3x2	—	—	— 2x2	—	—	—
No. 2 L.M.	— 3x3	— 3x3	— 1x1	— 3x3	— 2x2	—	—	—	—
No. 3 McC.	—	—	X	—	—	X	—	—	X
No. 4 F.T.	— 2x3	— 3x3	— 2x2	X	X	X	X	X	X
No. 5 F.E.	— 3x3	— 3x2	—	X	X	X	X	X	X
No. 6 L.O.	— 2x2	— 2x2	X	— 1x1	—	X	—	—	X
No. 7 D.	— 1x1	— 1x1	X	— 1x1	— 1x1	X	—	—	X
No. 8 F.O.	— 2x2	— 2x2	X	—	—	X	— 3x3	— 2x2	X
No. 9 L.E.	— 2x2	—	—	—	—	—	—	—	—
No. 10 M.M.	— 2x2	— 1x1	— 2x2	—	—	—	X	X	X
No. 11 M.	—	—	—	—	—	— 2x2	—	— 2x3	— 2x2
No. 12 S.	X	— 2x2	X	X	—	X	X	—	X
No. 13 V.	— 3x3	— 2x2	—	—	—	X	—	—	— 3x3

X — Never done.

what sanguinous colonic discharge and not biopsy tissue. Two of the three sources of the three antigens used presented ulcerative colitis complicated only by rectal stricture; the third, "O.L." presented no pathology other than that of an uncomplicated ulcerative colitis. This indicates that this substance may be in the lumen of the intestine without the necessary presence of elephantiasis, stricture or vegetations. Thus, ulcerative colitis may not only be brought about by dysentery and tubercle bacilli and E. histolytica, but also possibly by the virus of L.i., and probably by other viruses. The only reference encountered to work of a similar nature is that by Nicolas, Favre, Lebeuf and Charpy (7), who secured one antigen from the pus exuding from a fistula of one with ano-rectal elephantiasis with a positive Frei test. In three cases with positive Frei tests, this antigen gave positive responses. No control work of any nature is reported.

CONTROL STUDIES

One case (Chart VI, No. 6) showed a positive response at 48 hours, but was negative at 9 days; this was regarded as a foreign protein reaction because of its lack of persistence. Case No. 8 showed a positive skin reaction with unfiltered bowel antigen at five days, but was negative at twelve days. This was considered doubtful because of its lack of persistence. If one chooses to consider this reaction as positive, it is the only deviation in the thirteen controls tested. The intradermal response of "McK" 1:15 antigen in case No. 10 was negative at 48 hours and 9 days, but positive in 16. This unusually belated response cannot be satisfactorily explained. Even though Frei tests giving no significant reactions at 9 days are regarded as negative, this response has been classed as doubtful. In this connection it should be noted that the above cases No. 8 and No. 10 were found negative with the single active Frei antigen with which they were tested. It was impossible to secure their return for further intradermal studies with other known active Frei antigens. Incidentally, all other cases except case No. 1 in the positive group, were tested with more than one known active Frei antigen.

Due to insufficient unfiltered bowel exudate antigens from those with ulcerative colitis with positive Frei tests no control studies could be undertaken among those never having had colitis but who presented positive Frei reactions. Control studies with unfiltered bowel exudate antigens from ulcerative colitis cases and from other sources both with negative Frei tests have not been done. As has been noted elsewhere, it has been found impossible to date to procure additional antigens free from viable bacteria. Such attempts, however, are being continued. The securing of adequate antigens from only a few ulcerative colitis cases with positive Frei tests would seem to have been a fortuitous circumstance, since it is impossible to predict when, with the identical technique, another antigen will become available. In most instances the heat used to inactivate the possible virus or inciting substance prior to intradermal inoculation is insufficient to destroy all of the intestinal bacteria in such material. We are not oblivious to these shortcomings and are still attempting to overcome them.

CHART VI

Intradermal responses of those with and without ulcerative colitis with negative Frei tests to an antigen of unbowel exudate from an ulcerative colitis-positive Frei case

Controls "OL" Antigen									
	1:10			1:20			1:40		
Case	48 hrs.	9 days	14 days	48 hrs.	9 days	14 days	48 hrs.	9 days	14 days
No. 1 T.L.	— 3x3	— 4x3	— 4x4	—	—	— 3x2	—	—	—
No. 2 L.M.	— 2x2	— 4x3	— 3x3	—	— 3x3	— 3x3	—	— 2x2	— 2x2
No. 3 McC.	—	—	X	—	—	X	—	—	X
No. 4 F.T.	— 4x4	— 4x4	— 3x4	X	X	X	X	X	X
No. 5 F.E.	— 3x4	— 4x4	— 2x2	X	X	X	X	X	X
No. 6 L.O.	+ 5x5	— 3x3	X	— 3x3	— 2x2	X	— 2x2	— 2x2	X
No. 7 D.	— 3x3	— 3x3	X	—	— 2x2	X	—	— 2x2	X
No. 8 F.O.	* + 5x5	§ — 3x3	X	— 4x4	— 2x2	X	— 3x3	— 2x2	X
No. 9 L.E.	— 3x2	—	—	— 3x3	—	—	—	—	—
No. 10 M.M.	— 3x3	— 3x3.5	— 3x4	— 2x3	— 3x3.5	— 3x3	—	— 2x2	— 3x3
No. 11 M.	— 4x4.5	— 3x3	— 4x3	— 3x4	— 2x3	— 2x3	— 1x1	—	— 2x2
No. 12 S.	X	— 3.5x3	X	X	— 2x2	X	X	— 2x2	X
No. 13 V.	— 3x3	— 3x3	—	— 4x3.5	— 3x3	— 4x3	— 2x2	— 2x2	—

X — Never done.
* — Read on 5th day; §—Read on 12th day.

The significance of this work rests in the suggested presence of a virus which may bear a likely relationship to the etiology of one type of ulcerative colitis. These findings bring into being the further likelihood of the presence of other viruses in the alimentary apparatus. These may clarify the present uncertain etiologic knowledge of many phases of digestive disease.

SUMMARY

There is reason to believe that some cases classed as idiopathic or non-specific ulcerative colitis, with or without stricture, may be due to a virus or viruses. Cases of ulcerative colitis of undemonstrable etiology were selected in whom the possible presence of a virus in the colon might be etiologically related to the colitis as suggested by their having positive Frei reactions. Attempts were made to prepare antigens of bowel exudate for intracutaneous tests in accordance with the Frei technique. Filtering this material through Berkfeld V and N and Seitz filters resulted in the obtaining of antigens giving negative responses. Unfiltered bowel exudate antigens were prepared from three cases of ulcerative colitis, two with stricture and one without, presenting positive Frei tests and negative intracutaneous responses to the Ducrey bacillus antigen.

There were obtained striking intracutaneous responses of 5 mm. or more in diameter, persisting for at least 9 days in six ulcerative colitis cases with positive Frei tests, and negative responses in at least 12 of 13 control cases with and without colitis and with negative Frei tests.

The significance of these cutaneous allergic responses, paralleling positive reactions with known active Frei antigens, suggests the presence of an inciting agent unlike a toxin, a specific bacterium or foreign protein, possibly a virus or viruses, within the intestine of man. This may bear a relationship to the etiology of one type of ulcerative colitis, and brings into being the likelihood of the presence of other viruses in the digestive apparatus. These may clarify the present uncertain etiologic knowledge of many phases of digestive disease.

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DISCUSSION

DR. H. NECHELES (Chicago, Illinois): Dr. Paulson demonstrated that persons with a positive Frei reaction

(F.R.) and colitis have a substance in their colons which produces a positive Frei reaction in this same group. This brings up several questions: Can it not be that all of these six patients have had lymphogranuloma inguinale (L.I.)? In the literature cases have been described with slight L.I. and with no suppuration. Many more such unrecognized cases with positive F.R. may occur and in some colitis may develop accidentally.

A positive F.R. signifies a certain immunity against the virus. It is thinkable that after the healing of the L.I., the virus may persist in the colon of these persons, especially women (were the patients male or female? white or colored?). Therefore, it seems to me the question has to be answered whether persons with a positive F.R., but not suffering with colitis, harbor this virus in their colons.

The virus of L.I. is not known. The proof that it may cause colitis so far is circumstantial. Therefore the following questions must be asked.

a. Can one produce colitis with virus of L.I.?

b. Can material from the colons of persons with colitis and positive F.R. cause L.I. in man and encephalitis in animals.

Clinically and pathologically both diseases are very different. Colitis is a disease of the mucosa. L.I. is a disease of the lymphglands.

French authors, especially, have stressed the effectiveness of antimony therapy in L.I. If this is true, good results ought to be obtained also in colitis with positive F.R.

One must not forget that besides the theory of bacterial or virus causation of colitis there is a yet unanswered physiological side to it. I am thinking of the importance of the colon as excretory organ and as organ sensitive to changes in intermediary metabolism. Changes of permeability through abnormal excretions, changed pH, pathological intermediary metabolism, may produce inflammation and ulceration of the colon, and the host of organisms present in the colon may then produce a secondary infection.

Colitis patients frequently represent a certain nervous type of person, and hypermotility of their colons may indicate an increased number of nervous impulses to it. I have found the colon to respond more to acetylcholine (a.c.) than the upper G.I. tract. Stimulation of parasympathetic nerves produces a.c.; a.c. effects strong contractions of the colon and possibly, as we have been able to show in the case of the stomach, vasoconstriction. This may be followed by focal necroses, autolysis or digestion, and secondary infection by the host of bacteria always present in the colon.

DR. MOSES PAULSON (closing the discussion): I do not mean to infer that a virus has been actually isolated. I mean only to state that a substance or substances has been found in the colonic exudate from some with ulcerative colitis and positive Frei tests, which when prepared after the manner of the Frei antigen, give intracutaneous reactions paralleling the positive Frei responses. The colonic exudate antigen responses do not seem to be due to the antigenic qualities of specific bacteria, a toxin or to foreign protein. It is my supposition that they represent an immunological reaction to substances of a virus character. This allergic response may be in consequence either of the virus of lymphogranuloma inguinale or of other viruses or substances giving a like response. In this connection, the mere presence of a virus would not in itself mean that it is the cause of the disease with which it appears associated. My purpose here was to demonstrate a product in the human intestine unlike any with which we have heretofore worked. Eventually such may throw new light upon some of the digestive manifestations of obscure etiology.

In answer to the question as to sex and color—five of the six were women, and five of the six were colored.

The Diagnostic Significance of Anti-Dysentery Bacteriophage*†

By

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THE possibility that certain types of seemingly nonspecific chronic enteritis and colitis may be in fact chronic bacillary dysentery has increased interest in diagnostic procedures. It has long been known that anti-dysentery bacteriophage is commonly encountered in the stools of patients convalescent from the acute form of the disease. Recently the significance of this lytic principle in chronic infections has been investigated, and the term "diagnostic bacteriophage" has been introduced. Felsen (1) has obtained the "diagnostic bacteriophage" from certain cases of chronic ulcerative colitis. Similarly Winkelstein and Herschberger (2) found a phage present in 36% of 41 cases of ulcerative colitis, and absent in 45 miscellaneous controls. This finding they state "seems to have some significance" and they conclude "The finding of a bacteriophage active for one or more strains of bacillary dysentery organisms, is indirect but suggestive evidence that the patients have had or are suffering from bacillary dysentery."

The specificity of action of unadapted bacteriophage obtained from stool filtrates is open to question. According to d'Herelle (3) each bacteriophage that may be isolated in nature possesses a mosaic of lytic activities and each of these may vary in degree. He has stressed the seemingly fortuitous character of the range of bacterial species lysed by any given phage. One race of bacteriophage may be active only against certain strains of E. coli, while a second may exhibit in addition lytic activity against E. typhosus or S. dysenteriae or both. Burnet (4) likewise states that very few phages have their activity limited to a single bacterial species, and many are capable of attacking a wide range of intestinal bacteria. Others (5) state that a lytic principle active against S. dysenteriae

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frequently can be isolated from individuals not suffering from dysentery.

AUTHOR'S STUDY

We began a study of the diagnostic significance of anti-dysentery bacteriophage several years ago in the course of an investigation into a possible relationship between chronic bacillary dysentery and non-specific ulcerative colitis. We (6) encountered a lytic principle in 34% of a group of cases of chronic ulcerative colitis and in 10% of ninety control cases. Our experience was summarized as follows: "It is impossible to evaluate the significance of bacteriophage. While it is present in a considerably larger number of cases of ulcerative colitis, it occurs frequently in the absence of demonstrable infection by B. dysenteriae. Similarly it was found in a small proportion of the control group apparently free from infection." Further experience has confirmed our original statement and suggests the necessity for strict qualification of the term "diagnostic bacteriophage." In view of this it has seemed desirable to present our observations in detail.

TABLE I—GROUP I

Incidence of bacteriophage in cases with positive culture or agglutinins

Total Cases: 84	Bacteriophage Present	Bacteriophage Absent
Positive culture	8	15
Agglutinin titre 1/160 or above, negative culture	8	24
Agglutinin titre below 1/160, negative culture	6	23
Totals	22	62
Incidence of Bacteriophage in entire group		26.2%
Incidence of Bacteriophage in cases with good evidence of S. Dysenteriae infection		29.1%

One hundred and seventy individuals have been studied. They comprise a considerable group of cases of chronic ulcerative colitis, a small number of intestinal protozoal infections and a large number of miscellaneous conditions. For the purposes of this investigation they have been divided into two groups. The first group includes all cases presenting positive culture or demonstrable agglutinins against Shigella dysenteriae in their blood. The second group comprises those cases who afforded neither cultural nor serological evidence of infection by these organisms.

METHOD

Approximately 3 c.c. of freshly passed fecal material were emulsified in 50 c.c. of sterile meat infusion broth pH 7.3 to 7.4 and incubated over night at 37° C. Gross suspended matter was then removed by centrifuge and the supernatant fluid was filtered through a Berkfeld filter. 0.5 c.c. of the filtrate was then added to tubes containing 3 c.c. of lightly seeded 3 hour broth cultures of our laboratory strains of *S. dysenteriae Shiga* serological variants of Flexner, and Sonne-Duval. A second set of broth tubes, inoculated at the same time with the homologous strain but without subsequently added filtrate, were set up as controls. Both sets of tubes were then incubated at 37° C. and observed at intervals up to twenty-four hours for clearing of the turbidity. The stock strains of *S. dysenteriae* used were further tested for freedom from autogenous bacteriophage by the plate method.

RESULTS

Group 1 includes eighty-four patients from whom positive cultures were obtained, or whose sera contained demonstrable agglutinins for strains of S. dysenteriae, irrespective of the titre. No cases of acute bacillary dysentery are included. All the cases with intestinal symptoms were clinically chronic and in numerous instances positive cultures, and, or, positive agglutination reactions were obtained repeatedly. An anti dysentery bacteriophage was present in the feces of 22 of these, an incidence of 26.2%. If cases with negative culture and low titre agglutination reactions are excluded and the group is thus restricted to those individuals who present acceptable evidence of infection by S. dysenteriae the incidence of bacteriophage is increased to 29%. (Table I).

TABLE II—GROUP I

Cases with bacteriophage and positive culture or agglutinins

Total Cases: 22	Cases	Culture	Agglutinin Titre 1/160 or Above	Agglutinin Titre Below 1/160
Achlorhydria	1	0	0	1
Acute Salpingitis	1	1	0	0
Amebiasis	1	0	1	0
Bacterial Endocarditis	1	0	1	0
Ulcerative Colitis	18	7	6	5
Totals	22	8	8	6

Eighteen of the twenty-two cases from whom an active lytic principle was obtained were suffering from chronic ulcerative colitis. Positive cultures were obtained from seven of these patients. Six showed an agglutinin titre of 1/160 or above. The primary diagnosis in the remaining cases were respectively: achlorhydria, intestinal amebiasis, subacute bacterial endocarditis, and acute salpingitis. One of these apparently was a symptomless carrier of a Flexner strain and two of the others showed partial agglutination of a mannite fermenter at a dilution of 1/160. (Table II).

TABLE III—GROUP II CONTROLS

Incidence of bacteriophage in cases without evidence of infection by S. Dysenteriae

Total Cases: 86	Cases	Bacteriophage Present	Bacteriophage Absent
Ulcerative Colitis	25	6	19
Intestinal Protozoal Infections	8	1	7
Miscellaneous Conditions	53	4	49
Totals	86	11	75
Incidence of Bacteriophage	12.8%		

The *control group* comprises 86 cases who gave negative cultures and whose sera contained no demonstrable agglutinins for our laboratory strains of *S. dysenteriae*. Twenty-five of these were cases of ulcerative colitis, eight were intestinal protozoal infections, and fifty-three were miscellaneous conditions, clinically not suggestive of bacillary dysentery. Anti-dysentery bacteriophage was present in the feces of eleven of these patients, an incidence of 12.8%. (Table III).

TABLE IV

Incidence of bacteriophage in miscellaneous conditions without acceptable evidence of infection by S. Dysenteriae

Total Cases: 16	Bacteriophage Present	Culture	Agglutinin Titre
Achlorhydria	1	0	1/80
Acute Appendicitis	1	0	0
Arsphenamine Hepatitis	1	0	0
Foreign Body in Liver	1	0	0
Intestinal Protozoal Infection	1	0	0
Ulcerative Colitis	6	0	0
Ulcerative Colitis	5	0	Less than 1/160
Total	16 Cases		

DISCUSSION

Certain obvious sources of inaccuracy are recognized. The technique of bacteriophage determination is not standardized. Our methods, although differing in some respects, in general are comparable with those used by others who have carried out similar investigations. It is probable that the plate technique would reveal a higher incidence of lysis. Such a control was not practicable. Pure line S and R dissociants of our cultures were not used. Felsen has emphasized the necessity for repeated search for phage. In the majority of our cases this was not done. However, when repeated determinations were made on the same case, the results were often considerably at variance at different times. We recognize that the incidence of bacteriophage obtained in this study is therefore below that which would be anticipated, had we investigated our cases more completely. On the other hand this does not affect the question at issue: the validity of anti-dysentery bacteriophage determination as a diagnostic measure.

This experience therefore casts considerable doubt upon the diagnostic significance of bacteriophage in chronic intestinal infections when it is unsupported by corollary evidence in the form of positive culture or significant agglutination titre.

We have not been impressed by the incidence of specific bacteriophage in association with chronic bacillary dysentery. Only 29% of the cases with acceptable evidence of infection by S. dysenteriae exhibited a lytic principle active against these organisms. An anti dysentery bacteriophage was found accompanying positive culture in only 34.7% of our cases.

Moreover our experience leads us to question seriously the specificity of such a lytic principle. A phage active against our laboratory strains was obtained in 12.8% of the control cases. None of these could be suspected of infection by S. dysenteriae on cultural or serological grounds, and with the possible exception of the cases of chronic ulcerative colitis, none could be suspected on clinical grounds. We have found anti-dysentery bacteriophage in our control cases in association with such diverse conditions as achlorhydria, acute appendicitis, arsphenamine hepatitis, foreign body in the liver, intestinal protozoal infection, and chronic ulcerative colitis. (Table IV).

CONCLUSIONS

1. Anti-dysentery bacteriophage was found in only 29.1% of 55 cases presenting acceptable evidence of chronic infection by S. dysenteriae.

2. An anti-dysentery bacteriophage was found in 12.8% of 86 miscellaneous control cases none of whom presented evidence of infection by S. dysenteriae.

3. The clinical and bacteriologic significance of anti-dysentery bacteriophage in chronic intestinal infections is not as yet sufficiently well defined to justify the term "diagnostic bacteriophage."

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DISCUSSION

DR. MORRIS L. RAKIETEN (Brooklyn, New York): I believe that Dr. Mackie has pointed out in his paper the specific objections that one who is interested in the phenomenon of bacteriophage would subject it to. I agree with Dr. Mackie that at the present time the term "diagnostic bacteriophage" is a misnomer.

If there are any phages that are particularly easy to isolate from a wide variety of sources, from fish aquaria, from drinking water, from gastro-intestinal contents of normal as well as sick individuals and from sewage, it is dysentery bacteriophage.

Dr. d'Herelle has isolated many thousands of so-called dysentery bacteriophages in the last 20 years, and I believe that he has not more than three so-called specific dysentery phages against *Shigella dysenteriae*. Most of them have typhoid, parathyhoid, coli, as well as most of the dysentery organisms.

So, when one claims to have isolated a dysentery bacteriophage, that particular claim is open to objection.

Now, it is one thing to assume as did d'Herelle, Dr. Costa Cruz, Pasricha, and Morrison, those particular investigators being interested in fields where dysentery is epidemic, especially in South America and in India, and to have shown that in cases of epidemic dysentery, that with convalescents one can demonstrate a bacteriophage; and with a demonstration of that bacteriophage a disappearance of the organism; but it is another thing to state, when one does find a so-called dysentery bacteriophage in the stool that one had to have previous infection with dysentery organisms.

Now, most of the papers that have dealt with the so-called diagnostic bacteriophage—I refer to Dr. Mackie's as well as Winkelstein's, Felsen's—are open particularly

to the objection that the method that they use for demonstrating bacteriophage is the crudest method of demonstrating bacteriophage, the so-called test-tube method. It is only when isolated bacteriophage is of the maximum potency that one gets what one may call complete clearing in the test tube.

Many bacteriophages that are moderately virulent may not appear in a test-tube method. Those particular bacteriophages will be passed over since the tubes inoculated with the filtrates containing the bacteriophage will be as cloudy as the control tube.

A better and a cheaper and a much more efficient method of demonstrating bacteriophage is by a so-called cross test in which one takes susceptible cultures and tests the filtrates against these particular cultures on agur plates.

(Slide) This slide, I believe, points that out a little better. If you will notice here are some bacteriophages which lyse this particular strain, and here are the bacteriophages that lyse that one. You will notice as compared to this particular plaque that those areas are filled with colonies, and while the bacteriophage is able to manifest itself against a particular strain according to this test it does not completely lyse it as this one and that one does, but one finds these particular so-called secondary colonies.

In a test-tube method that particular phenomenon will show up as complete turbidity and might be read by investigators as no bacteriophage at all in that particular test tube.

Now, while I say that is a much better and a cheaper method than test-tube demonstration, the best method of demonstrating bacteriophage is by the so-called plaque demonstration.

(Slide) This is a strain of bacterium coli which has been inoculated with bacteriophage in these various segments. All of these bacteriophages have been diluted out to about 10-11. Now, one finds that these bacteriophages, especially this bacteriophage here, if it is clear to you, consists of these very light areas which are plaques and which are considerably different from the plaques in this particular segment. As a matter of fact, if you were close enough you could see in this segment that we would have more than one type of plaque. Some of these are large and some of these are considerably smaller.

Yet, while that is bacteriophage, if that was done in a test tube, it would show up as completely turpid as to control.

The next objection which I want to point out is the method of isolation. The best way of demonstrating bacteriophage is to take the sewage, or stool and add to it some broth. To this particular broth you add the culture for which you want to demonstrate bacteriophage. If bacteriophages are there only in small amounts they may be absorbed by dead susceptible organisms or completely overgrown by other phages. If one adds the susceptible culture for which one wishes to demonstrate bacteriophage, it does give the bacteriophage present in that sewage a chance to manifest itself.

Until more accurate methods are utilized both for isolation and demonstration, I believe the term "diagnostic bacteriophage" should be held in abeyance, especially since we know that so-called dysentery bacteriophages are probably the least specific bacteriophages that we know anything about.

DR. ASHER WINKELSTEIN (New York City): Although I have enjoyed the speaker's paper very much, I disagree with his conclusions.

The question which Dr. Mackie brings up is whether the finding of a dysentery bacteriophage in the stool is valid evidence that the patient has or had bacillary dysentery. The best evidence for bacillary dysentery is the finding of the dysentery organism in the stool and its agglutination by specific sera. Even the presence of agglutinins in high titre in the blood is only suggestive evidence.

The findings of d'Herelle, Felsen, and myself, indicate that the dysentery bacteriophage is important diagnostically. Although we have already published our findings on this subject, I wish to show one slide illustrating our studies. (Slide) We found a dysentery bacteriophage in 15 out of 41 consecutive cases considered clinically typical non-specific ulcerative colitis. In seven of these cases the phage appeared as the patients were recovering and disappeared when they were well, thus fulfilling d'Herelle's criteria of the recovery mechanism in bacillary dysentery.

Then we studied 45 consecutive controls, including several miscellaneous diarrhaes, and they did not show any dysentery bacteriophage.

From Dr. Mackie's own statistical evidence it seems that approximately a third of his cases had the phage, and that it was almost completely absent in his controls. It does not seem fair to include the 24 cases of ulcerative colitis in his controls because it may be that those cases had bacillary dysentery without the presence of a bacteriophage. Also, its complete absence in our 45 controls does indicate that it may be suggestive evidence.

Now with reference to the other point about the polyvalency of the phage. Nearly everyone has a weak B. Coli bacteriophage in the stool. It is certainly possible that under certain conditions, such as the presence of a colitis, that this phage may take on stronger properties and lyse not only the colon bacillus but dysentery bacilli and other organisms.

In order to test this hypothesis, in our recent colitis cases with a dysentery phage in the stool we set up this phage against the patient's own colon bacillus and against stock strains. Lysis did not occur. This would indicate that the bacteriophage is specific, at least in these cases, for the dysentery strains.

Therefore, we believe that a better conclusion would be both from Dr. Mackie's findings and our own studies, that when one finds an anti-dysentery bacteriophage in the stool of a non-specific ulcerative colitis patient that it should suggest the probability that that patient's disease is related to bacillary dysentery.

DR. JOHN L. KANTOR (New York City): I have nothing to add specifically to the technical points that have been brought out so conscientiously by the previous speakers. They have added several links to one aspect of the problem.

But I think we should continue to regard this question with a broadminded attitude. When several years ago the bacteriology was stressed as the solution of this problem, I pointed out, in discussion, what had been pointed out previously by Dr. Thomas Brown and many others, that other possibilities were still open, that for example the question of a metabolite circulating in the bodies of certain individuals and then causing damage to mucosa on its excretions was still to be considered. The same point was stressed by Dr. Necheles this morning.

May I call attention to the fact that certain bacteriologists are now engaged in the demonstration of the specific importance of the bacillary dysentery organism? Would it not be well for the Council to invite Dr. Felsen next year to produce evidence from the epidemiologic angle that ulcerative colitis may begin as a specific bacillary dysentery?

Briefly, he believes that bacillary dysentery is epidemic in this country and that the phase of specific infection is a very short-lived one, and that it is the rule for the bacteria to disappear from the stools in the first week or so and it is the exception to find them later. Repeated stool investigations, such as those that Dr. Mackie has so brilliantly performed, will give a fairly high incidence of dysentery "carriers."

We should also look to the psychologic make-up of these colitis patients. Dr. Sullivan last year pointed out something about their personality. I disagreed with one phase of his presentation as I understood it. It is nevertheless

a possibility that by psychologic tests we may be able to recognize certain individuals who are susceptible, either to their own metabolites or to specific germs that the rest of us throw off although we may be infected by them.

Dr. Lichtwitz, at the Montefiore Hospital, has been concerned about the metabolic aspect of these patients and has made some interesting observations. It is true that the altered metabolism is more likely to be a result than a cause of the disease, but we should learn about that also.

In other words, this Association shall keep an open mind as to the nature of this crippling disease and study it from all possible angles.

DR. BURRILL B. CROHN (New York City): It may be purely an accident that most of the speakers on this subject are from New York City. The interest in the relationship between bacillary dysentery and the so-called non-specific ulcerative colitis is still an open problem to all of us.

There is no question about the widespread distribution of bacillary dysentery throughout the country. The reason I stress New York City is because the Board of Health of New York City has notified us in a letter that in the year 1934 they had 365 cases of bacillary dysentery in Greater New York and in the year 1935, up to November, they had something like 590-odd cases.

In addition to that the files of the Public Health Service of the United States show bacillary dysentery prevalent throughout all the states of the United States. There are no states that are exempt. States like Massachusetts and Pennsylvania seem to have continuous case reports of bacillary dysentery.

Of course there is one criticism to all of these reports—*no one knows exactly what constitutes a diagnosis of* "bacillary dysentery." Nothing short of a definite finding in the stool of bacillus dysenteriae gives meaning to the agglutinins. We have obtained reports of agglutination reactions of from 1:160 or 1:180 or much higher, but what the significance of the specific agglutination means, is open to question. If the relibility and the pathological and normal limits of agglutination could be decided, and if a group of bacteriologists could determine what the agglutination significance is, then we could very soon determine what bacillary dysentery is and shortly we would know whether there is a relationship between bacillary dysentery and so-called non-specific ulcerative colitis.

DR. DONOVAN BROWNE (New Orleans, Louisiana): My knowledge and experience with bacteriophage is certainly inadequate. However, I have been impressed by the statements made by some of the discussants. First, that of accepting the isolation of a dysenteriae organisms from the feces of a patient as diagnostic of bacillary dysentery, and second the significance given an agglutination of 1 to 160.

About three years ago we made a rather careful survey in our particular section of the country, New Orleans. Groups were selected from various sections of the city which gave no history of dysentery or digestive disturbance. The feces were repeatedly cultured and the agglutinins in the blood for the dysenteric groups determined. That we were able to isolate one or more of the dysenteriae organisms in 8% of the normal individuals is very interesting. The most frequently encountered organism was the lactose fermenter of Duval. The bacillus of Shiga was rarely isolated but the most surprising feature of the study was the frequency with which the blood of normal individuals agglutinated stock cultures of *Bacillus dysenteriae*. This was particularly true of the less virulent groups such as the *meta dysenteriae* of Castallani and the Duval lactose fermenters. In certain instances, the normal blood titre ran as high as 1 to 300; this being so we are rather cautious in accepting agglutination of 1 to 160 as diagnostic of *B. dysenteriae*, except with the Shiga and possibly the Flexner groups, in which the agglutinins are apparently more specific.

The single isolation of an organism of the dysenteriae groups from the feces or obtaining a positive agglutination of stock culture of Bacillus dysenteriae in dilutions of 1 to 160 is not in all instances sufficient evidence to warrant a diagnosis of bacillary dysentery.

DR. T. T. MACKIE (closing the discussion): I shall go through the points that have been raised seriatem.

As is indicated by the title of our paper, the objective was an attempt to evaluate the significance of a lytic principle as a diagnostic measure pointing to present or *past contact of the individual with Shigella dysenteriae.*

In dealing with chronic infections, we have only three possible diagnostic measures available. One is the demonstration of the organism recovered from the patient's intestinal tract. The second is the demonstration of reacting substances in the patient's serum, which are generally accepted as evidence of a biologic association. The third is the so-called diagnostic bacteriophage.

I am in complete agreement with the view of the discussers that the significance of any given agglutinin titre is open to considerable question. Yet, when one is faced with the necessity of classifying cases, an arbitrary standard has to be accepted as a working basis. We originally chose the titre of 1 to 160, because of the experience of several British workers who have studied this question intensively.

The object of this paper was to raise a discussion not of the significance of the agglutination reaction in chronic bacillary dysentery, but of the specificity of anti-dysentery bacteriophage.

Certain Aspects of the Applied Physiology of External Pancreatic Secretion*†

By

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EFFECTS OF EXCLUSION OF PANCREATIC JUICE FROM THE INTESTINE

DIGESTION and absorption: The most certain method for permanently excluding the pancreatic juice from the intestine in an animal is to tie the pancreatic ducts and then to separate the organ from all its connections with the duodenum (1-3). When this is done in the dog, one observes polyphagia, the passage of large bulky stools containing undigested and unabsorbed starch, protein and fat, and a gradual loss of weight in most instances unless special attention is given the diet.

The polyphagia is associated with a more rapid emptying of the stomach, which is probably a result of

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the partial starvation incident to defective intestinal digestion and absorption (4). The polyphagia is very obvious and persists indefinitely, for at least a year or longer (1-6). Associated with this a hypernormal secretion of gastric juice may occur (4). A hyponormal secretion has not been observed experimentally except in poorly nourished animals. A detectible compensatory increase in the secretion of enzymes in the *succus entericus* does not occur (7).

The passage of bulky stools is observed early, provided post-operative complications, which cause anorrhexia, are absent. The stools (dry weight) as a rule are more bulky than those of obstructive jaundice (1-4) or sprue (1). The digestion and absorption of protein are affected slightly more than that of fat, that of carbohydrates being least affected (6). The deficiency varies considerably in different animals and to an appreciable extent in the same animal, the cause of the variation being unknown. I suspect the variations are due to differences in the emptying time of the intestine ("intestinal time"). On increasing the quantity of food, total absorption is increased, but the efficiency of absorption is diminished (6). Some dogs with exclusion of pancreatic juice from the intestine withstand the deficiency when fed an average stock diet much better than others (1-6). Unless some special attention is given the diet, the majority lose weight progressively. More recent observers find that if raw pancreas is added to the diet nutrition may be maintained for more than a year. We (2,3) have maintained six animals in an excellent condition for more than a year, by feeding 200 gm. of raw ground pancreas daily. The same is true of the majority of depancreatized dogs. Yet, an occasional depancreatized dog may be maintained in a good condition on insulin without receiving pancreas for a year or more (8, 9), if given a high vitamine diet. Handelsman, Golden and Pratt (6) studied three dogs with exclusion of pancreatic juice. All three animals received a diet containing a liberal amount of carbohydrates and milk fat. The one not receiving brewer's yeast died in three months of inanition. The two receiving the same diet, plus yeast, lived in good condition for eight months and two years, respectively.

We (10, 11) have observed more than one hundred dogs in which the pancreatic juice and bile are emptied into the last six inches of the ileum. These dogs suffer from a deficiency of intestinal digestion and more than 90% of them lose weight. The administration of raw pancreas and gastric mucin definitely improved the nutrition of 40% of twenty such dogs. The feeding of a special diet high in nuclear substances, vitamines, milk fat, and readily assimilable carbohydrates maintained the nutrition of 60% of the dogs, for 10 weeks or longer, or until they developed jejunal ulcer. This special diet fed to similarly operated dogs, which had in addition from two-thirds to three-fourths of the fundus of the stomach removed, thus suffering from a deficiency of both pancreatic and gastric digestion, 51% of thirteen dogs remained in excellent condition for more than one year, and six of the thirteen remained in excellent condition for more than two years.

The special diet consisted of:

A prepared stock dog food		400 grams
Percentage composition		
Cooked wheat and barley flour	75%	
Dried milk	10%	
Tomatoes	5%	
Bone meal	5%	
Cod liver oil	5%	
Fresh whole milk		200 grams
Raw ground pancreas		300 grams
Raw ground liver		200 grams
Corn syrup		100 grams
Banana flour		50 grams
Total		1250 grams

The dogs were fed all of this diet they would ingest, and some dogs ate as much as from four to six pounds daily. The fecal wastage was obviously very high.

We agree with Pratt and others that patients affected with pancreatic deficiency should receive a liberal diet, high in easily assimilable carbohydrates and emulsified fat (milk), enough protein being fed so that sufficient is absorbed to maintain a positive nitrogen balance. Fats with lower melting points are somewhat better digested than are those with higher melting points, probably because of easier emulsification (12).

Oral enzyme therapy in pancreatic deficiency: The effectiveness of orally administered pancreatic enzymes has not received general acceptance, because doubt exists as to whether they may pass through the stomach without being inactivated.

Prior to 1912 the literature (13) contained a few carefully studied patients who exhibited pancreatic deficiency, in whom the administration of raw pancreas and pancreatin decreased the fecal loss of fat and nitrogen. Very little clinical investigation has been reported since then. However, in 1925, Silverman, Denis and Leche (14) studied the effect of oral administration of pancreatin and raw ground pancreas on the duodenal concentration of enzymes in a human subject. Their results showed that pancreatic preparations taken by mouth enhance the digestive power of duodenal contents. We (2) have recently found, in a study of the effect of the oral administration of malt amylase to ten human subjects, that when it is mixed with a cereal meal an average of 51% of the enzyme passes into the intestine before it is inactivated. The gastric digestion of starch is also appreciably augmented. Malt amylase was used because it is inactivated at a lower pH than salivary or pancreatic amylase.

Experimentally raw pancreas has been added to the diet of depancreatized dogs because of its enzyme content. However, very little work has been done to ascertain if it is really effective in this regard. Pratt, Lamson and Marks (1) fed pancreatin to two dogs (9.6 gm. and 18.0 gm. daily) with a separated pancreas and observed a decrease in the nitrogen and fat lost in the stools. Nasset, Pierce and Murlin (15) fed pancreas (10-20 gm. daily) to two depancreatized dogs and observed an increase in nitrogen absorption.

To determine how effective taka-diastase and malt amylase are when given orally, we (Schmidt, Beazell and Ivy) have separated the pancreas from the duodenum in five dogs, placed them on a high cereal (82% farina) diet, containing 62% starch, and after suitable control periods have fed the enzymes, the starch loss in the feces being followed by a quantitative method. The

average starch loss during the control period was 24.2% in five dogs. The administration of malt amylase (35 gm. daily; 50 gm. of Ovaltine, having a U. S. P. potency or slightly higher) daily reduced the average starch loss to 14.0%. Taka-diastase (25 gm.; U. S. P. potency or slightly higher) reduced the average starch loss in three dogs from an average control loss of 27.4% to an average of 15.6%. The dry weight of the feces was also decreased.

Thus, there can be little doubt as to the oral effectiveness of enzymes administered in the presence of pancreatic deficiency. We (2) have shown that it is best to give some enzyme with the meal and then some in water just after the meal. Pancreatic enzymes might also be given between meals, if given in some buffered solution as milk to buffer the acid in the stomach.

Liver: In connection with the exclusion of pancreatic juice from the intestine, it is important to bear in mind that depancreatized dogs receiving only insulin are very prone to develop hepatic insufficiency due to infiltration of the liver with fat. This is prevented by feeding raw pancreas, lecithin or choline (for references see ref. 13). Whether fatty infiltration and degeneration of the liver occurs when the pancreas atrophies as a result of fibrosis or obstruction of the ducts has not been demonstrated to my knowledge. Yet, the implied importance of administering lecithin containing foods to patients suffering from pancreatic deficiency should be remembered.

We (16) have recently found that within three weeks after ligation of the pancreatic ducts, or separation of the pancreas from the intestine, the capacity of the liver to form sugar from protein (gluconeogenesis) is impaired.

Berg and Tucker (17, 18) observed morphologic liver changes to occur from two to three weeks after duct ligation or pancreatectomy, and sooner when all the pancreatic juice was drained externally.

BLOOD ENZYMES AND EXCLUSION OF PANCREATIC JUICE

Amylase and lipase: It is established that obstruction of the pancreatic ducts or any disturbance which causes a passage of pancreatic enzymes into the blood and lymph results in a marked rise in serum amylase (liquefying) and lipase (emulsified-oil-splitting). The marked rise lasts for a few days only, some animals possibly showing slight rises from time to time for a longer period (1 or 2 months). Rises in serum lipase and amylase also occur in liver disease, but the rises observed are slight in comparison to those of acute pancreatic disease.

It would appear that only the visocometric or starch-iodine methods (Wohlgemuth), which detect the early stages of the hydrolysis of starch (liquefying), should be employed to test for serum amylase in pancreatic disease. This is because Reid and Narayana (21) found no increase when using reducing sugar methods (saccharogenic amylase) (22). In pancreatic disease, emulsified-oil-splitting lipase should be determined; a serum esterase determination by the ethyl-butyrate method has no significance (19).

Serum phosphotase is very high in obstructive jaundise in man and dog (23-26). It is also elevated markedly in catarrhal jaundice (24). Freeman and Ivy (23) have found it to be markedly elevated when only one hepatic duct is obstructed (33% of liver tissue) and the icteric index normal. We have also found that ligation of the pancreatic ducts or separation of the pancreas from the intestine causes only a slight temporary rise in serum phosphotase.

Thus, it is possible to diagnose acute involvement of the pancreas in the presence of obstructive jaundice. If serum amylase, lipase and phosphotase are all high, the liver and pancreas are both obstructed. If the phosphotase is very high and the amylase and lipase only slightly elevated, the liver is involved and the pancreas only slightly, if at all. If serum amylase and lipase are high and phosphotase low, the pancreas is more acutely involved than the liver.

However, it must be remembered that serum phosphotase remains high as long as hepatic obstruction persists and that serum amylase and lipase are high only for a relatively short period after obstruction of the pancreas. Hence, in chronic pancreatitis, a determination of serum enzymes is of little value, and one must rely on the results of the examination of either the duodenal contents or the stools.

FUNCTIONAL TESTS OF EXTERNAL SECRETORY ACTIVITY OF PANCREAS

I suspect that a deficiency of external pancreatic secretion occurs more frequently in man than is now believed. The pancreas appears to be less influenced by secretory nerves and nervous states than the stomach. Yet, its enzyme output is thought to be controlled more by nerves than by the hormone secretin. The hormone causes a copious flow of a thin secretion relatively low in enzyme concentration, although in man and dogs we (27) have observed an increase in total output of enzymes. However, the secretion of the pancreas is markedly reduced by very small amounts of epinephrine (28); and if the discharge of epinephrine by the adrenals is augmented sufficiently by emotion or anxiety, we should expect pancreatic secretion to be reduced. It would also be reduced by excessive splanchnic vasoconstriction.

In regard to functional tests, the question of the *factor of safety* of the organ deserves first consideration, because the factor of safety must first be destroyed before most functional tests show the presence of a deficiency. Very little work has been done on the factor of safety of the acinar tissue of the pancreas. We (28) have studied the response of the pancreas to secretin after excision of various parts. Excision of only a small portion of the tail or head of the pancreas results in a definite decrease in response. Thus, when secretin is the stimulant, the response is directly proportional to the amount of acinar tissue. We found further that functional regeneration of acinar tissue does not occur within two months. This is in contrast to the stomach in which organ excision of two-thirds of the fundus decreases the response to histamine and later the fundus hypertrophies (three to six months) and a normal response to histamine is obtained.

Destruction of acinar tissue only reduces the total capacity of the gland to secrete to a stimulus, and this can happen without a reduction of the enzyme concentration. So, on analyzing duodenal drainage in chronic pancreatitis, one must consider the factor of dilution of the pancreatic secretion, which as secreted may have a normal concentration of enzymes, by bile, duodenal juice and gastric fluid (the latter can be ruled out by testing the reaction of each ten minute specimens and discarding them if acid or only slightly alka-

line, or by draining the stomach with a second tube). Because of the dilution factor, we have never placed much emphasis on the concentration of enzymes in duodenal drainage, and have placed emphasis on the total output of enzymes over a period of time. However, we believe that the absence of, or the existence of, a markedly reduced enzyme concentration in duodenal drainage, the drainage being alkaline (pH 7.5 to 8.0), especially after stimulation, is significant. But, we do not believe a normal concentration or only a slightly reduced concentration is significant. In this connection I personally consider many of the findings of McClure and his colleagues, and of others, as significant.

Most of the foregoing data and discussion, however, is obviously not applicable to the question of how much of the acinar tissue of the pancreas has to be destroyed in order to obtain defective digestion and absorption of food. The data and discussion is not applicable, because we know that considerable digestion and absorption occurs when all the pancreatic juice is excluded from the intestine. Oddly this question has not been studied by direct experimentation with the employment of adequate methods. That is, no one has fed a standard test-meal and then extirpated portions of the pancreas to ascertain the amount that must be removed to cause fecal wastage. With the data available on the effect of complete exclusion and considering the apparent fact that the capacity of the pancreas to secrete is directly proportional to the amount of acinar tissue, one may make theoretical predictions. On the average carbohydrate diet in the dog, approximately 90% of the pancreatic amylase secreting tissue would have to be removed before starch would appear in the feces. On a high cereal diet (62% starch) approximately 66% of the pancreas must be removed. On an average fat diet, about 66% must be removed; on a high fat diet, about 50% must be removed. On an average protein diet, about 55% must be removed; on a high protein diet, about 40%.

Whether one may obtain more reliable data for practical purposes by examination of the feces than by duodenal drainage, I believe is an open question. Several years ago we (27) injected secretin intravenously into twenty-two presumably normal medical students with a duodenal tube in place. We found that some individuals may manifest a low secretion of one enzyme and not the others. The secretion of trypsin was most uniform. Amylopsin was most easily exhausted apparently, but lipase was more consistently low than the other enzymes. In two subjects the lipase was so low as to appear to be abnormal. So, these two subjects were fed a meal consisting chiefly of one-half pound of rare beef and 60 c.c. of olive oil. Both subjects manifested steatorrhoea, but not creatorrhoea.

I suspect that secretin may be found to have the same relative merits in a test of pancreatic secretory function that histamine has in a test of gastric secretory function. It should be obvious, however, that the results of a secretin test or of duodenal-drainage analysis may not be a test of the efficiency of intestinal digestion, because, although pancreatic juice plays a very important *rôle*, other factors are concerned such as the quantity and quality of intestinal juice and bile, and intestinal time or motility, and the normality of the absorptive process. Fecal analysis can be the only practical and reliable method for testing the efficiency of intestinal digestion.

Some day a dye may be discovered which will be specifically eliminated by the pancreas and which will provide us with information concerning the volume output of secretion, but more than one hundred dyes have been examined in my laboratory and none found to be of practical worth.

As a standard test-diet for the study of digestion and absorption in pancreatic and intestinal disease, that of Adolph Schmidt (21, 1) should be mentioned. Space does not permit its discussion.

PANCREATIC SECRETION IN JAUNDICE

It has been suggested (30) that the cause of the soapy stool in jaundice is due to a failure of the pancreas to be stimulated because bile is "the alimentary stimulus for pancreatic secretion." While it is true that bile of proper reaction in the duodenum stimulates the pancreas, it has been shown that either common duct obstruction (31) or the drainage of all bile to the exterior (32) does not reduce the secretion of the pancreas. Thus, the soapy or fatty stool of jaundice is not due, as chemical analyses confirm, to disturbed pancreatic digestion but due to *disturbed absorption*. The disturbance of absorption is due to the absence of the important *rôle* that bile salts play in rendering fatty acids soluble in aqueous solution at the slight acid reaction commonly found in the intestine.

FOODS AND PANCREATIC SECRETION

In providing nourishment to patients having pancreatic fistulae, subacute or non-fatal acute pancreatitis, or in which the pancreatic juice has been excluded from the intestine as in the Whipple operation for carcinoma of the head of the pancreas, it is important not to give foods which stimulate pancreatic secretion. In acute pancreatitis patients should not be fed orally, as a matter of fact it is usually impossible because of vomiting and collapse.

Glucose intravenously does not stimulate the pancreas (36), neither does saline solution, in my experience, unless given in quantities sufficient to cause a hydremic plethora. All agree that taking most any substance by mouth with the exception of alkalies stimulates pancreatic secretion. I teach that foods which stimulate the formation of gastric juice and cause the gall bladder to contract are those which in general stimulate the pancreas most. According to Pavlov meat and bread are about equally potent, and fats and milk rank second. Acids such as found in gastric juice and fruit juices stimulate. Water stimulates and alkalies decrease (33, 34, 37). My own experiments would cause me to list the foods in order of potency as follows: meat, first; milk and fats, second; white bread and carbohydrates, third (38, 39). Wohlgemuth (34) and Holsti (35) rank carbohydrate first. Wohlgemuth introduced a low carbohydrate diet (antidiabetic) with large amounts of sodium bicarbonate for the treatment of pancreatic fistula. Some have obtained good results, others bad. It is my opinion that we do not know which foods stimulate the pancreas most or least, or whether foods have a specific effect on enzyme content of pancreatic juice as claimed by Pavlov. I believe a statistical study is required to settle this matter because of the variations reported.

(For a review of human pancreatic fistula cases see ref. 40).

Time and space do not permit a discussion of such topics as: (a) the effects of loss to the outside of pancreatic juice, (b) the decrease sugar tolerance found in pancreatitis, (c) the *rôle* played by pancreatic juice *vs.* bile in the development of "peptic ulcer," (d) the *rôle* of pancreatic secretion in the regulation of the reaction of the stomach, intestine and blood; (e) fat necrosis; (f) etiology of pancreatitis; (g) pain in pancreatic disease; and (h) pancreatic secretion in sprue and coeliac disease.

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DISCUSSION

DR. JOSEPH H. PRATT (Boston, Massachusetts): We have been able to produce experimental acute pancreatitis in dogs without the introduction of bile, intestinal juice or stomach contents. This has been accomplished by simply tying the pancreatic ducts and separating the pancreas from the duodenum by the insertion of the omentum between the two. This procedure was devised by Dr. Fred T. Murphy, as Dr. Ivy has stated, for shutting out all pancreatic juice from the intestine. In a considerable proportion of animals on which this operation was performed fatal acute pancreatic necrosis developed with the death of the animal in two or three days.

The claim has been made by a number of German writers, chiefly surgeons, that the presence of a pancreatic lipase in the blood is diagnostic of acute pancreatitis, and that the lipase is also increased in cancer of the pancreas. In several of our dogs with occluded pancreatic ducts the atoxyl-resisting lipase was determined in the blood and no significant increase found.

In 39 cases of various diseases Dr. Magendantz of our staff determined the amount of pancreatic lipase by the stactometric method of Rona and Michaelis. In this series there was no case of acute pancreatic necrosis but four of cancer of the pancreas. In none of these was the atoxyl-resisting lipase present in a significant amount. On the other hand a relatively large amount of this lipase was present in other diseases, namely, abscess of the liver and obstructive jaundice. An increase was also present in syphilis and in angina pectoris uncomplicated by abdominal disease. In the method we used the splitting of tributyrin was measured. Crandall and Cherry found in the blood a lipase capable of splitting a true fat (olive oil) after the pancreatic ducts were tied. We hope to use their method in further experiments.

Golden and others in our laboratory have determined the amount of diastase in the blood in ten dogs after occluding the pancreatic ducts. The improved method of Wohlgemuth was used. Previous to the operation 2 to 64 units of diastase were present in the blood. Twenty-four hours after the pancreas was separated from the duodenum the diastase increased in the blood of all the dogs. The smallest rise was to 256 units, the average over 500, and the largest 2048 units. The diastase curve usually reached its highest point on the second or third day after the operation. When obstruction of the ducts was permanent the amount of diastase usually remained above the normal level. In one dog 825 days after the operation 256 units were still present. If the obstruction is overcome by the formation of sinuses the level of blood diastase quickly drops to normal. Our results show that if there is obstruction of the pancreatic ducts the blood diastase will rise. From the experiments the conclusion cannot be drawn that in acute pancreatitis the blood diastase will be high. If an increase is found in acute pancreatitis it is, I believe, evidence of a retention of pancreatic juice within the ducts. In a case of cyst of the pancreas Dr. Golden found a large amount of diastase in the blood.

Dr. Ivy is correct in his statement that total obstruction of both pancreatic ducts is rarely seen clinically. When it does occur it is characterized by the passage of bulky stools

while the patient is on a full diet. I am sorry that the use of the Schmidt diet seems to be out of fashion. When it is employed much can be learned in the diagnosis of pancreatic disease from the gross and microscopic study of the stools. When no pancreatic juice enters the intestine the weight of the dried stools is greater than in any other condition. With normal digestion Schmidt found that the average weight of the dried feces during a period of three days on his diet averaged 54 grams. In a case of obstructive jaundice we found that the weight of the dried feces during three days on the Schmidt diet was 131 grams, while in four cases of total occlusion of the pancreatic ducts the weight was over 400 grams.

The chemical analysis of the stools is very time consuming and requires a skilled worker. In the recognization of occlusion of the pancreatic ducts I urge the value of the simple procedure of determining the weight of the dried stools. If Schmidt's standard diet is used for a three days' period it will be possbile to compare the results obtained with those of Schmidt and other workers. If the weight of the dried feces is 300 grams or more it is almost conclusive evidence of total obstruction of the pancreatic ducts.

DR. JULIUS FRIEDENWALD (Baltimore, Maryland): I should like to direct attention to the cases of pancreatic diseases reported some years back by Doctor Cullen and myself. Of these there were four instances of acute pancreatitis, fifteen of chronic pancreatitis, seven of pancreatic cysts and thirty-seven of carcinoma.

In all of the acute pancreatic cases, the patients had been affected with previous attacks of indigestion complicated by the presence of gall stones and biliary colic. The attacks began with sudden violent abdominal pain referred to the epigastrium. Diabetes was present in one patient, in another there was a subsequent abscess formation. Fat necrosis occurred in all. Three of the patients recovered following operation; one died.

In the cases of chronic pancreatitis the symptoms were indefinite but this disease may be suspected if in a patient having chronic dyspepsia there is present epigastric pain often to the left of the mid-line and not infrequently referred to the left shoulder blade associated with nausea, vomiting, emaciation, weakness and slight jaundice. In more advanced cases, intermittent glycosuria, hyperglycemia, bulky soft fetid stools aid in arriving at the diagnosis. In our cases of chronic pancreatitis there was a history of chronic indigestion in eleven and biliary colic in five. Our greatest aid in the diagnosis is derived from the examination of the duodenal contents for pancreatic ferments, the activity of which is markedly diminished in this affection.

In our cases of pancreatic cysts there was present a prolonged history of indigestion and abdominal discomfort with colicky pain; as the cyst enlarges the pain becomes pronounced. The pain may be located in the epigastrium but is often referred to the back or may be in the right or left hypochondrium. The most distinctive sign in our cases was the progressive enlargement of the tumor between the xyphoid cartilage and the umbilicus. The mass produced a protrusion in the median line but most frequently in the left hypochondrium.

In the diagnosis of carcinoma of the pancreas as we have found the following associated signs and symptoms of importance: (1) Digestive disturbances, (2) presence of a tumor and the enlargement of the gall bladder, (3) symptoms produced by involvement of the pancreas itself and by pressure of the growth upon neighboring organs.

It is of interest to note, that at times when operating fór gall stones, the surgeon may discover a large hard and often nodular mass in the region of the head of the pancreas which may lead to the diagnosis of cancer. His diagnosis may be incorrect; the hard nodular mass may be due to a chronic pancreatitis. In a small group of cases, however, the very reverse is true, the mass may be considered in the light of a chronic pancreatitis when it may finally be proven to be cancerous.

Attention is directed to a small though definite group of cases in which according to our experience the definite signs are preceded by a persistent diarrhea. The patient may at times complain of loss of appetite, nausea and vomiting but without pain. Constipation which is usually present at first is rapidly transformed into a diarrhea which becomes more and more excessive and finally fatty stools appear. After a shorter or longer period of time jaundice manifests itself which gradually becomes more and more pronounced. This symptomatology occurs frequently enough to warrant the conclusion that whenever a persistent diarrhea is observed in individuals during or past middle life which cannot be accounted for by the usual causes, carcinoma of the pancreas should be suspected.

DR. THOMAS R. BROWN (closing the discussion): I should like to say just a few words. First, I want to reiterate the importance of the abdominal symptom upon which Dr. Jones has touched, that is the presence of deep abdominal pain in the left hypochondrium at about the level of the gall bladder, sometimes associated with deep tenderness in this region. And second, that we must not forget it is essential to study the stool from every angle as it may give us clues which we constantly miss if we fail to carry out this procedure.

Diseases of the Pancreas -- The Clinical Aspect*

By

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BALTIMORE, MARYLAND

THE pancreas is a much neglected organ. When one realizes the enormous *rôle* played by the external secretion of the pancreas in the digestion of all the foodstuffs and its close relationship—geographical, vascular, lymphatic, nervous — with stomach, duodenum, gall bladder and transverse colon, all organs in which a great deal of pathology is found and diagnosed, we must conclude either that the pancreas is an organ singularly immune to disease or that in the majority of cases we do not recognize its pathology, organic or functional.

I am sure the latter is true. I am quite sure a considerable number of vague upper abdominal syndromes,

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sometimes only with gas, distension and discomfort, sometimes also with true pain, are due to this cause, especially in older people where the chances of infection, vascular change and sclerosis are of course obviously increased.

One has many reasons for this belief. First, the number of cases in which changes in the pancreas are found when the abdomen is opened for other causes and where the surgeon finds an unsuspected pancreatitis, sometimes the only finding, and therefore the obvious cause of the symptoms that no one had suspected were pancreatic in origin; second, though this of course is much less frequent, the times when we find evidence of fat necrosis when the abdomen is opened, obviously representing the aftermath of a previous and unrecognized acute or subacute pancreatitis; and third, the fact that the pancreas is supplied with autonomic nerves and that these are susceptible to the same disturbances met with in any other portion of the sympathetic system—local, reflex or psychogenic in origin.

There is of course definite experimental evidence in favor of this, for although Starling and Bayliss feel that in explaining pancreatic secretion, the mechanism of a special hormone could explain the whole phenomenon, this obviously cannot be true. In the first place, Pavlov, Koschinsky, and many others have shown that by stimulating the pancreatic nerves, a definite pancreatic secretion is brought about. In the second place, it can be shown in experimental animals that severe shock can produce a complete pancreatic achylia. Finally, the fact that in true gastric achylias, when no hydrochloric acid whatsoever is found and when therefore the normal mode of stimulation of changing prosecretin into secretin is absent, the pancreatic secretion may be, and usually is, absolutely normal. In these cases this must be brought about by nervous, not chemical, stimuli. We have found this to be true, for instance, in cases of pernicious anemia and various other conditions where a complete gastric achylia is shown by histamin stimulation and fractional meals. We have made these tests both by the study of duodenal contents and the more accurate, if properly done, though much more difficult quantitative estimation of the pancreatic ferments in the stool.

What do we diagnose sometimes correctly — and sometimes incorrectly? The relative parities — pancreatic cyst, pancreatic carcinoma, acute pancreatitis. What do we almost always fail to diagnose? Practically all cases of the much more common chronic and mild subacute pancreatitis, and, in all probability, the major proportion of the functional disturbances.

As to *pancreatic cysts*—degenerative, traumatic, inflammatory—and pseudo cysts—round or oval tumors, usually in the midline just about or above the umbilical region, usually increasing, though slowly, in size, occasionally fluctuating, more often tense, with occasional spontaneous changes in size—this is the usual picture to be differentiated from mesenteric or retroperitoneal cysts or even solid tumors in this area, and of course to be treated surgically with marsupialization.

Pancreatic carcinoma is most frequently found in the head of the organ, with the classical picture of progressive painless jaundice, rarely a palpable tumor in the earlier stages at least, usually associated with an enlarged gall blader with the usual general symptoms of any form of malignant neoplasm—progressive loss of weight and strength, occasionally with symptoms very suggestive of carcinoma of the transverse colon. And yet not always this classical picture for the growth is not always in the head of the pancreas and jaundice may be absent. It is not always painless as in some cases pain, especially severe left back pain, is common even in the early stages of the disease, though of course much more frequent later when it may be very severe. The gall bladder is not always enlarged for its walls may be so thickened by the chronic cholecystitis, with or without stones, which is so frequently associated with pancreatic disease, that distension is impossible.

And again, the classical picture may be absolutely simulated by painless *common duct stone* or by *cirrhosis of the head of the pancreas*. In the former case the true diagnosis may sometimes be suspected by noting periods where the jaundice is lessened, associated with a slight transient pigmentation of the stool. In the latter case, even the surgeon is frequently unable to make a differential diagnosis at the time of the operation, usually a cholecystgastrostomy, and only time can answer the question—in the one case, death, albeit a bit belated; in the other, progressive improvement and return to health.

Unquestionably there is frequently a disappearance of the pancreatic ferments in duodenal contents or in stool—the bulky stool—in cases of carcinoma of the head of the pancreas. How much of this is due to destruction or dysfunction of the glandular tissue due to the disease, how much is due to a complete obstruction to the pancreatic duct, how much to the associated chronic and progressive jaundice with its increasingly inhibitory effect upon glandular secretion, is hard to say. I believe, however, the obstructive factor is the largest factor as I have seen a few cases of carcinoma of the pancreas without obstruction to the common duct and without jaundice, in which the pancreatic ferment readings were quite normal. It is very probable that the pancreas, like the liver and possibly many other organs, has a large margin of reserve and can produce a practically normal secretion even where there is considerable destruction of certain portions of its substance as in carcinoma.

If one wishes to visualize every phase of the progressive downhill course of carcinoma of the head of the pancreas in its classical form, may I recommend a novel by the great French physician-novelist, Paul Bourget, "The Night Cometh."

Acute hemorrhagic pancreatitis, one of the acute abdominal catastrophies, presents in its earlier phases at least a picture far more suggestive of a profound toxemia than of an infection or inflammation: exquisite epigastric pain and tenderness with very little muscle spasm, profound prostration and shock, circulatory collapse with thready pulse, little or no increase of temperature or white blood count at first—somewhat suggestive of high ileus. Of course when the inevitable inflammation and infection set in, the picture changes and the condition is therefore frequently diagnosed as perforated gastric ulcer, severe gall stone colic, perforation of the gall bladder or high intestinal obstruction.

And yet the picture rarely lacks some suggestive diagnostic sign or symptom if we but search carefully for it, especially if the patient has given a previous history of gall bladder disease, which is so frequently associated with this condition. Although usually occurring in people of middle or later life, it is occasion-

ally met with in very young children. It practically never occurs in those whose gall bladders have been previously removed. The cause may be the rare trauma, the commoner infection, possibly some other factor, the infection arising usually from a diseased biliary tree, possibly with an increase of biliary pressure. Many have believed that the infected material is retrojected directly into the pancreatic ducts and canaliculi. The recent work or Rich, however, shows that the biliary pressure under no condition becomes so high as that in the pancreatic secretory system, makes this method of infection much less probable. Infection, therefore, if it plays a *rôle*, takes place probably directly through the lymphatic system.

But whatever the cause, the effect is the same—trypsin zymogen is activated, autolysis takes place, and a group of toxins of extreme potency is elaborated; toxins peculiarly affecting the circulatory apparatus—hence the extreme vascular collapse so characteristic of the disease.

Rich also has shown that there occurs a constant and specific vascular lesion with rapid necrosis of the walls of arteries and veins—the direct result of the action of the trypsin upon them, and that the pancreatic hemorrhage results from the rupture of these necrotic vessels. He shows too, that the majority of cases result from potential obstruction to the outflow of the secretion in the smaller ducts, that this obstruction is usually due to metaplasia of the epithelium and that attacks are peculiarly likely to occur after a large meal or after alcohol.

If the disease is recognized and surgery performed—that is, drainage of the destructive ferments or cholecystectomy—some cases die, some get well. If operation is not performed, perhaps because the condition is not recognized, perhaps because it is not of extreme severity, perhaps because some surgeons believe that nature, not the knife, gives better results, some recover with extensive areas of fat necrosis; a few, a very few, develop suppuration and gangrene with that remarkable picture — a pancreatic abscess, a tumor, steadily increasing in size and when opened showing bits of necrotic pancreatic tissue floating in the pus. It is extremely uncommon and rarely diagnosed correctly. Dr. Halstead once said that he should like, above everything, to make such a diagnosis before he died, but his wish was not gratified. He saw only two cases, in neither was pancreatic disease suspected and the true pathology only determined by the exploratory operation.

Pancreatic calculus is extremely uncommon and rarely diagnosed correctly, the attacks of pain almost exactly simulating those of gall stone colic without jaundice. If the condition is suspected, however, the diagnosis may possibly be made by stool and urine studies, there being an absence or marked diminution of pancreatic ferments in the former and an enormous increase in the latter. We established this urinary normal of diastase in 1914 and in the one case of pancreatic stone we have diagnosed, the amount of urinary diastase was increased more than twenty times. Incidentally, the quantitative estimation of diastase in the urine is a good test of renal function except, of course, in those cases where there is jaundice or obvious pancreatic disease, and the readings run practically parallel with the phenosulphonphthalein readings, as Rowntree and I found in that same year.

Chronic pancreatitis rarely is diagnosed but I believe is frequently present. I am quite sure that some of the vague upper abdominal syndromes met with in people of middle or later life are of this origin. The condition probably represents either a sclerosis or a low grade of infection originating from a diseased gall bladder.

Unquestionably the most common source—is gastritis, a duodenitis, possibly from the large bowel. In most cases it is probably through the lymphatic channels. But it may occasionally represent a direct extension from disease in the vicinity, such as peptic ulcer or cholecystitis. All of us of course have seen definite cases of perforation of peptic ulcer into the substance of the pancreas. Sometimes a suspicion of pancreatitis may be made more probable by certain laboratory findings—an alimentary glycosuria, changes in the stool, preferably with the patient on a Schmidt diet, with abnormal amounts of undigested fats or starch or meat fibres. Sometimes a real azotorrhea, sometimes a true butter stool with more than one-half the ingested fat unabsorbed and of this, 50% or 60% in the form of neutral fat.

Certainly marked disturbance in fat digestion, the absence of jaundice, diarrhea, is very suggestive of pancreatic disease, because almost all of the fat splitting ferment is found in the pancreatic secretion, only minimal amounts in gastric contents or in intestinal juice. Some have lain stress upon the presence of undigested nuclei in the stool if bits of thymus or muscle fibre are given by mouth, as the pancreas is the main, if not the only, source of nuclease.

But none of these tests is absolutely diagnostic because we always have a number of variables—differences in the motor and absorptive powers of the intestine, the possibility of vicarious enzymes from other sources and possibly the effect of enzymes of bacterial origin, to confuse the picture.

We have found a considerable diminution, though not complete absence of pancreatic ferments in the stool or duodenal contents, of help. In the case of diastase, for instance where by our method the readings for normal individuals vary between 600 and 2400 starch gram units, our figures ran between 120 to 300 units in cases of definite chronic pancreatitis. We know, of course, from definite animal experiments that there is a definite quantitative and possibly qualitative response of the pancreatic secretions to food. Obviously we cannot study our cases from pancreatic fistula as we can in animals, hence there are many possible errors in the estimation of these ferments in both duodenal contents and stool. Nevertheless, I believe the results obtained thereby are of real value, especially in the case of diastase and trypsin, if all sources of error are reduced to an "irreducible" minimum and the most meticulous care employed in carrying out every test.

With the possibility of pancreatitis in our minds, with the careful analysis of symptoms and with the use of some or all of these laboratory tests, I feel that pancreatitis can probably, if not absolutely, be diagnosed in many more cases than obtains at present. I am equally sure that, just as in the evolution of cirrhosis of the liver, we may have attacks of pain sometimes so severe as to simulate gall stone colic, yet entirely of inflammatory origin and probably due to acute exacerbations of the infectious process, so in the pancreas we may find a similar picture—pain, sometimes severe pain, which suggests obstruction of some kind

but which in reality probably represents a small acute transient process in the course of the slowly progressing degenerative, sclerotic or infectious process which is called "chronic pancreatitis."

As regards treatment, pancreatic ferments by mouth, the minimizing of infection elsewhere and the proper diet, especially one limited as to fats, unquestionably help certain of these cases. I have always felt in this connection, that it is probable that in certain cases of cholecystitis, with or without stones, the benefit that follows from a fat low or fat free diet is not all due to its effect upon the biliary infection, but is rather due to the effect of this diet upon the associated pancreatic disease or dysfunction so frequently associated with gall bladder disease. In my experience, if gall bladder disease, even cholelithiasis, is not associated with jaundice or pancreatic trouble, the simpler fats, butter, cream, olive oil and especially egg yolk are in reality our most valuable dietetic aids in promating gall bladder drainage and should be used in large amounts.

Are there *functional disturbances* of the pancreatic external secretion? There must be, for the pancreas is supplied with autonomic nerves which unquestionably play some, if not the major, *rôle* in stimulating or inhibiting secretory activity and therefore there certainly must be examples of hypo-, hyper-, and achylia-pancreatica of this origin. But its diagnosis is obviously extremely difficult; probably in most cases impossible, for while we may suspect it, it is very hard to differentiate from mild chronic pancreatitis, just as it is equally difficult or impossible to differentiate certain functional gastric disturbances from a mild gastritis, although the gastroscope may settle this question.

I have seen a few cases, however, in which I think the diagnosis was absolutely justified. Let me report one—a woman who had been operated upon many years ago and eighteen gall stones removed from the gall bladder. When seen by me fourteen years later, she had definite recurrent gall stones attacks and I had her operated upon with a removal of the gall bladder filled with stones. The pancreas was found perfectly normal at the time but a few days after the operation she developed an intractable diarrhea with typical butter stool and complete absence of pancreatic diastase and trypsin. Time, diet, possibly helped by the administration of pancreatic extract in large amounts, cleared up the condition; in a relatively short period of time, the diarrhea stopped, the stool regained its normal character. That the pancreatic trouble was purely functional, I think was shown beyond question not only by the rapid return to normal of the stool and the reappearance of pancreatic ferments in the fecal material, but by the fact that in a subsequent operation made about three months later for adhesions, the pancreas was examined carefully and found to be just as normal as it had been at the time of the preceding operation. If diarrhea follows cholecystectomy, as it does in a very small proportion of cases, it is probably often of this origin.

In thinking over the problems of the pancreas, one cannot fail to ask himself certain questions not answered in this rapid survey of our experience in this field. The most important is—is the pancreas an absolutely essential organ? Apparently not as regards its external secretion for proteolysis can be brought about by the pepsin and hydrochloric acid of the stomach, the erepsin, and possibly other ferments of the small intestine, and possibly by bacterial action. There is diastase from the salivary glands with minimal amounts from Brunner's glands and the bile to carry on starch digestion. The fats, however, will fare rather badly for lipase is derived almost exclusively from this organ and fat digestion is practically always impaired in extensive pancreatic disease or dysfunction. But, after all, good health may be maintained on a high carbohydrate, high vitamin, normal protein, low fat diet.

There is clinical as well as experimental evidence that the pancreas is not absolutely essential. Functional pancreatic achylia with its butter stool, if treated with the proper diet, does not seriously affect the general health. Even in organic conditions where there is complete absence of this secretion, such as in a few cases of tropical sprue, a certain number of cases of cirrhosis and many cases of carcinoma of the head of the pancreas, death does not come early but at long last. Certainly in cases of carcinoma of the pancreatic head, the symptoms in the early stages—malaise, depression, pruritus, chills and fever, even pain—are not due to the cancer *per se* but are symptoms of a progressive jaundice with biliary toxemia. Thus the marvelous temporary improvement after cholecyst -gastrostomy or -duodenostomy! There is experimental evidence also in favor of this. For instance, in 1912, in a series of experiments made upon dogs with pancreatic fistulas, we found that as long as they were given plenty of fluids and plenty of alkali, their condition remained extremely good for a long period of time. If, on the other hand, the common biliary duct was subsequently ligated and a complete obstructive jaundice produced, in every case this was followed immediately by rapid loss in weight and strength and early death, emphasizing anew the great importance of the bile as a partial substitute for the pancreatic secretion if the latter is absent or markedly diminished.

These findings — clinical and experimental — are really of great significance for they justify partial or complete pancreatectomy for carcinoma. The salivary, gastric and intestinal secretion, and bile, possibly helped by pancreatin by mouth, will act as substitutes for the external secretion; insulin, possibly some day, pancreas transplantation, for the internal secretion.

Is pancreatic disease more common than is supposed or diagnosed? I am sure so. Can it be recognized or suspected more frequently than at present? I believe so, if one but keeps in mind its possibility in all cases with vague upper abdominal symptoms, with and without pain, and then utilizes all possible diagnostic procedures.

Perhaps there is no better way to end this fragmentary talk on the clinical aspects of pancreatic disease than to repeat what was said by Sir Archibold Garrod many years ago—"The chief difficulty in diagnosing disease of the pancreas is in thinking of the pancreas."

Surgical Aspects of Diseases of the Pancreas*

By

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IN a paper read before the New England Surgical Society in September, 1921, on "Acute Pancreatitis," I said that the term would probably always be used but that I would try to show that it was not descriptive enough and that the terms *acute pancreatic necrosis* or *acute hemorrhagic necrosis of the pancreas*, and *acute and chronic interstitial pancreatitis* would describe the various conditions found more accurately. I can find no reason for changing this opinion in spite of the fact that no one seems to have followed my suggestion.

Archibald (Lewis' "Practice of Surgery") has helped matters very much by dividing pancreatic cases into six groups, as follows:

(1) *Hyperacute pancreatic necrosis.*
(2) *Acute pancreatic necrosis.*
(3) *Subacute pancreatic necrosis.*
(4) *Acute pancreatic oedema.* (Zoepffel)
(5) *Chronic pancreatitis with recurrent subacute attacks.*
(6) *Chronic pancreatitis with sclerosis* (following acute attacks).

So far as dividing these cases into definite groups is concerned, this classification is of value, and if it were properly used we should not have such variation in the mortality statistics under the heading of acute pancreatitis as we have at present, when it varies from 22.7 per cent to 70 per cent or more. This great variation in mortality must be due to the variation in the type of cases used rather than to the difference in the skill of various surgeons.

My objection to this classification is that I believe there are two types of pancreatitis:

(1) Acute pancreatic necrosis, due to injury to the pancreatic ducts by retrojection of bile or duodenal contents into the pancreatic ducts, causing a digestion of the pancreatic parenchyma.

(2) An infiltration of the interstitial tissue with enlargement and an increased hardness and at times oedema. The condition may be either acute or chronic. The parenchyma of the gland is not involved. This should be known as interstitial pancreatitis.

With an idea in my own mind that the classification, etiology, pathology, symptomatology, and treatment of pancreatitis had been clarified to some extent, I was much disturbed to find that there was more confusion than ever about these points. It is impossible to discuss these cases until we can at least agree upon some classification, and classification cannot be agreed upon until the pathology has been agreed upon. Archibald has classified the cases of pancreatic necrosis, but what constitutes a pancreatitic necrosis? I have classified as pancreatic necrosis any case of pancreatitis in which there is fat necrosis or hemorrhage, because it is my belief that neither occurs without the release of activated pancreatic secretion which in turn causes pain and tenderness in the upper abdomen with nausea.

Archibald has a group which he calls chronic pancreatitis, which is due apparently either to very mild repeated attacks of pancreatic necrosis or to repeated attacks caused by the backing up of nearly normal bile into the pancreatic ducts, which he calls "subacute attacks of pancreatitis." He has still another group which he calls chronic pancreatitis with sclerosis, due to acute attacks of pancreatic necrosis, I assume, as only a necrosis could cause the amount of destruction he speaks of.

It has been my contention that there is an interstitial pancreatitis without involvement of the parenchyma, due to infection of the interstitial tissue. There are many cases of so-called interstitial pancreatitis of which there are no symptoms at any time, unless an abscess is formed and that seldom occurs. It is found only during the course of operation for other causes, such as cholelithiasis, peptic ulcer, or abdominal infection.

Three articles have been published recently in which various pathological changes have been classified under chronic pancreatitis and chronic interstitial or interlobular pancreatitis. Hinton (Annals of Surgery, September, 1932) states that duodenal and gastric ulcers in contact with the pancreas cause interlobular pancreatitis, which causes severe pain relieved at once by gastro-enterostomy. DeTarnowsky and Sarma (Annals of Surgery, June, 1935) describe *chronic pancreatitis* as a thickening of the gland due to repeated attacks of acute subsiding pancreatitis. Elman (Surgery, Gynecology, and Obstetrics, Nov., 1935) confuses the matter still more by reporting six cases of chronic *interlobular* pancreatitis, three of which had fat necrosis and three of which had no fat necrosis but had gall stones.

Under such conditions how is it possible to discuss chronic interstitial pancreatitis intelligently? I can only say that I myself have never seen a case of "chronic interstitial pancreatitis" without hemorrhage or fat necrosis diagnosticated before operation. Such conditions have no symptoms so far as I can determine.

The *mortality* of the two groups, acute pancreatic necrosis and chronic interstitial pancreatitis, is strikingly different. There is a mortality of at least 50 per cent in the cases in which the parenchyma is involved, while in the second group the mortality cannot be more than 2 to 3 per cent. If we accept Archibald's classification of acute pancreatic oedema (Zoepffel) as an acute interstitial pancreatitis, this would bring up the mortality rate somewhat. If, however, it is classed as acute pancreatic necrosis, as I believe it should be, the mortality rate corresponds accurately to the mortality rate of the acute pancreatic necrosis group.

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Not only are these two groups different in pathology, etiology, and mortality, but the two have entirely different symptoms. In the first group the patients are always operated upon because of symptoms due to the pancreatic necrosis or retrojection of nearly normal bile, while in the interstitial pancreatitis group they are operated upon because of symptoms due to biliary disease, duodenal or gastric ulcer (Hinton), or abdominal infections.

If we accept the division of these cases into the two groups, (1) acute and chronic pancreatitis due to activated pancreatic secretion or nearly normal bile, and (2) interstitial pancreatitis probably due to infection of the pancreas, and accept Archibald's division of the pancreatic necrosis cases into four groups, we can talk about the operative procedures and mortality of each.

There is some difference of opinion in regard to the type of operation to be performed. Archibald believes it necessary only to drain the biliary system. This appears logical, but what of the four autopsies reported by Opie some twenty-five years ago, in which the necrosis was limited to the area drained by the duct of Santorini which opened separately into the duodenum. While it is logical to drain the biliary system, there are undoubtedly a certain percentage of pancreatic necrosis cases due to retrojection of bile into the duct of Santorini. In fact, Opie states that the duct of Santorini is the main duct in 10 out of 100 autopsies.

The operative procedures for the various divisions of Archibald's classification should be settled in the minds of all surgeons. The extent of the operation should be determined by the condition of the patient. The very sick should have the least possible done; that is, drainage of the fatty capsule. If the surgeon believes it reasonable, a cholecystostomy with or without removal of stones may be done. Those in slightly better condition should have the fatty capsule and the true capsule, where soft areas are found, drained and a cholecystostomy done with removal of gall stones. In those patients in still better condition the gall bladder should be removed, the ducts explored, and a choledochostomy done.

It is self evident that drainage of the common duct will give freer flow than will drainage through the gall bladder, but it is necessary not infrequently to do a cholecystostomy because of the condition of the patient or because of the difficulty of reaching the duct.

Archibald does not approve of cholecystectomies for fear that the gall bladder may be needed for drainage later, but the great majority of surgeons do remove the gall bladder if the condition of the patient will permit it.

It is difficult to see the objection to drainage of the fatty capsule when it is infiltrated and tense and contains much broken down tissue. While I agree with Archibald in practically all of his work, I cannot agree that drainage of the biliary system is all that is necessary. I feel strongly that drainage of the fatty capsule, and the true capsule of the gland so far as it can be done without injury to the pancreas, is of great advantage to the patient. I have seen many patients relieved of pain and shock after drainage of the fatty capsule, and have had two very definite cases in which the patient remained uncomfortable, nauseated, and unable to eat after biliary drainage without drainage of the fatty capsule. Both were comparatively mild cases and both recovered after ten days which were very trying both to the patient and to the surgeon. I have never since neglected to drain the fatty capsule when there is swelling in the region of the pancreas, fat necrosis, or hemorrhage, no matter how slight.

It is true that drainage of the fatty capsule is more likely to cause an infection of the fat about the capsule than no drainage, but on the other hand proper drainage at the primary operation may prevent a secondary operation for the drainage of an abscess in this region. The neglect of early drainage of abscesses may, I believe, be responsible for some of the late deaths. When the fatty capsule is drained early, the patient frequently runs a moderate temperature or none at all for a week or ten days, at the end of which time the temperature rises to 101° or 103° with increased discharge of pus, broken down fat, and necrotic gland. A secondary operation is frequently necessary to give better drainage unless a large drainage wound is left at the first operation.

In addition to the difficulties of post operative drainage of the fatty capsule, these conditions not infrequently cause thrombosis of the veins in this region, not only the splenic vein but even the vena cava. The sepsis which is often present may cause infection in other regions, the same as any abdominal infection.

There have been changes in the minds of some surgeons recently in regard to the best time for operating on cases of acute pancreatic necrosis, largely because of the high mortality in these cases with our present method of so-called "early" operation. But are there enough cases operated upon within twenty-four hours to give us a proper idea as to the value of early operation? At the Massachusetts General Hospital early operation has largely been given up.

DeTakats and MacKenzie (Annals of Surgery, September, 1932) believe that:

(1) "Patients should never be operated upon in the initial shock," and yet their statistics show that the mortality in those cases operated upon within 24 hours is 25 per cent, the lowest mortality except for the group operated upon more than three weeks after the onset of symptoms. It may not be proper to operate within 2 to 6 hours after the onset, but it is a well known fact in surgery that removal of any condition causing shock will frequently save the life of the patient. The surgery must, of course, be reduced to a minimum. It is my belief, therefore, that all cases of pancreatic necrosis except the very mild should be operated upon at the earliest possible moment, first because of the possibility of an error in diagnosis, and secondly because I believe that there will be less destruction of tissue, and that the operation should be carried out under local anesthesia with a minimum of ether to keep the patient on the table during manipulation.

(2) "If all diagnostic measures point to pancreatic necrosis, delay is permissible until abscesses localize, cysts and gangrenous parts need removal." Yet their statistics show that operations delayed over 24 hours and up to 3 weeks have a mortality of 50 per cent. It is, I believe, important that all cases except the very mild ones be operated upon within 24 hours if it is possible to get the cases.

(3) "If diagnosis is uncertain, early operation must be done for fear of overlooking intestinal perfora-

tions." Operation within 24 hours would cover these cases.

(4) "If the attack is mild, wait for recovery and then diagnose and operate for biliary tract infection." Their statistics show that the mortality in cases operated upon more than 3 weeks after onset was only 20 per cent. It is quite evident that these cases were mild or operation would have been performed earlier. It would seem that the mortality of cases operated upon from 2 to 3 weeks after onset, 66 per cent, and the mortality of those operated upon after 3 weeks, 20 per cent, were unnecessarily high. It would seem reasonable to expect a lower mortality if all operations had been done within 24 hours.

May I diverge for a moment to mention *diagnosis* and to say that laboratory examinations, at least those in use up to the present time, should not make one give up physical examination, for every available method should be used in the diagnosis of these difficult cases. The most satisfactory aid to making such a diagnosis is the careful determination of the location of tenderness. It is not enough to say that there is tenderness in the upper abdomen. Given symptoms suggesting gall bladder disease, the diagnosis of pancreatitis should be made correctly in a high percentage of cases if there is tenderness extending to the left from the gall bladder. This can be accomplished only by meticulous care as to the amount and extent of the tenderness. Experience is necessary, of course, to make this distinction and yet a former resident, of very moderate hospital experience, made a correct diagnosis in the next two cases that were admitted after he had been taught this method of diagnosis.

I appreciate that there has been much written recently about attacks of pancreatitis causing pain, indigestion, and discomfort in the upper abdomen after cholecystectomies and cholecystostomies, but I have not seen enough of these cases to make me feel that pancreatitis following cholecystectomy and choledochostomy is of much importance. It is true that at operation I have left stones which have had to be removed at a second operation, but this has always given relief. I have operated twice for attacks of pain following operations for gall stones without finding any cause for the pain, even pancreatitis, but in spite of this there was no further occurrence of the pain after several years.

It is quite evident from various case reports that there is frequently more than one attack suggestive of pancreatitis before operation seems necessary. In 1921 I called attention to the fact that 22 of the forty-three cases of acute pancreatitis from the Massachusetts General Hospital occurred in patients without gall stones, and of these 17 had had one or more attacks of pain before having an acute attack of pancreatic necrosis requiring operation.

Archibald believes the mild attacks to be acute pancreatitis due to retrojection of nearly normal bile into the pancreatic duct, which causes an inflammation and therefore swelling, but not a necrosis. Whipple and Goodpasture (Surgery, Gynecology and Obstetrics, 1913, XVII, 591) report that in animals there may be attacks of pancreatic necrosis with absorption of the necrotic material which leave a scar so small that it is difficult to find it. How such a condition can produce the findings of deTakats and MacKenzie is difficult to understand.

"Indigestion" and slight discomfort in the epigastrium do not have much significance for me. When we consider the various operations which have been carried out for the relief of these symptoms, we wonder if these symptoms really mean much. The outstanding reasons given for such symptoms before operation have been chronic appendicitis, chronic salpingitis, retroversion of the uterus, so-called chronic cholecystitis without stones together with an X-ray showing a gall bladder which does not empty quite as the roentgenologist thinks it should, stasis in the duodenum, duodenal diverticulum, and now chronic pancreatitis either before or after operation. One is not much impressed with the value of these symptoms when they are supposed to be "cured" but such different operations. In many clinics chronic cholecystitis without stones makes up at least 50 per cent of all the gall bladder operations. One wonders why we do not all have our gall bladders out for slight indigestion and perhaps a fulness in the upper abdomen. It has been said by some surgeons that cases of chronic choecystitis without gall stones should be operated upon not only for relief of "indigestion," but also for fear they may cause pancreatitis! In spite of this great danger, Wilkie has said that he has had great difficulty in finding a bacteriologist who could find bacteria in the gall bladder walls for him, and yet he considers operation of great importance. If these symptoms are of value, why has it been necessary to do so many different operations for the relief of them, and why are patients not more often relieved by the operations?

Operations for the relief of acute interstitial pancreatitis do not seem to be necessary as the symptoms do not seem to be sufficient to make a diagnosis possible, or at least to make an operation necessary, as such a condition is rarely if ever seen at operation unless we consider Zoepffel's acute oedema of the pancreas as an acute interstitial pancreatitis.

The treatment of chronic interstitial pancreatitis is incidental to finding it in the course of operations for other conditions such as cholelithiasis, duodenal or gastric ulcer, acute cholecystitis, or some abdominal infection, and should consist, I believe, of the removal of whatever is the cause of the pain. To make doubly sure, it is important to drain the biliary system especially if there is jaundice. Many cases of chronic pancreatitis have been relieved entirely by cholecystectomy alone, without drainage of the biliary system. Long continued drainage of the biliary system has been emphasized by many surgeons, especially Deaver, but drainage for two weeks is sufficient in all the cases I have seen. Deaver recommended and carried out on several patients cholecyst-gastrostomy in cases in which jaundice had recurred or had not cleared. It has been my good fortune in about 2500 cases of cholelithiasis and cholecystitis never to have been obliged to do a cholecyst-gastrostomy for chronic interstitial pancreatitis. It seems probable that when any such operation is necessary, the condition present may be carcinoma of the head of the pancreas.

As to *preventive measures* in pancreatic disease, there is no doubt but that removal of gall stones when found is an excellent measure, but I cannot agree with those who feel that it is important to remove the gall bladder in cases of so-called chronic cholecystitis without stones, to prevent acute or chronic pancreatitis. The arithmetic of these men seems to me to be at

fault, for in my own practice I have operated upon forty cases of acute pancreatic necrosis and abscesses of the pancreas, while during the same period I have seen more than 2500 cases of cholelithiasis. That is, about 1.6 per cent of all the cases of cholelithiasis and acute cholecystitis are associated with acute pancreatic necrosis.

As the mortality of acute pancreatic necrosis is about 50 per cent, the mortality rate for these acute pancreatic necrosis cases associated with cholelithiasis and acute cholecystitis could not be more than 0.8 per cent. The operative mortality for cholecystectomy in cases of chronic cholecystitis could not be less than 2 per cent, which leaves a balance of 1.2 per cent in favor of not operating upon these cases.

While it must be admitted that there is little that is new in regard to the *treatment* of pancreatitis, we have a most brilliant piece of clinical work on carcinoma of the pancreas, for which we owe a debt of gratitude to *Drs. Whipple, Parsons, and Mullins, regardless of* whether the late results will or will not be commensurate with the brilliancy of the clinical deductions that have been made.

It must have been appreciated by every surgeon that pancreatic secretion could not get into the duodenum in cases of carcinoma of the head of the pancreas with marked jaundice, yet no one has ever before drawn the conclusion that the pancreatic duct might be tied off without doing any damage to the individual. This clinical observation has brought many cases of carcinoma of the pancreas into the field of operative surgery. Not only is the observation and proof that the patient can exist without the external secretion of the pancreas of importance, but the carefully worked out operative procedure is of great importance. (Whipple, Annals of Surgery, October, 1935).

It has taken many years to convince surgeons that the pancreas can be operated upon the same as any other organ, provided one is careful to prevent leakage and infection. In fact, it has been found that the pancreas can be incised or large sections removed without danger to the patient. To have this proof that patients can live with the pancreatic duct tied off gives the surgeon control over the whole pancreas. A large part of the tail can be removed from the tail toward the head without doing harm, and now that Whipple, Parsons, and Mullins have proved that the pancreas can be partly removed from the head toward the tail, the whole organ is under control.

Not only is this work of importance in carcinoma, but it will make the removal of cysts much more certain than formerly. Removal of a portion of the pancreas with the cyst may be done with the hope of no further trouble, for few have attempted to remove cysts of the pancreas with any feeling of certainty that they would not recur. With our present knowledge of the pancreas, removal of sufficient gland tissue to make sure that a cystadenoma or a simple cyst will not recur is of importance. Degeneration cysts or pseudocysts should not recur, and simple drainage is all that is necessary.

Probably the most spectular operations on the pancreas are those for hypoglycaemia due to adenomata or to hyperplasia of the pancreas. In addition to the adenomata, which give such striking results when removed, there is apparently a hyperplasia similar to hyperplasia of the thyroid gland. Some cases have been operated upon in which no adenoma can be found. In order to treat these cases, an unexpectedly large proportion of the gland must be removed, as in thyroidectomy, in order to reduce the insulin sufficiently to return the patient to normal. Unfortunately the problem is more difficult than in thyroid disease because of the greater risk in opening the abdomen two or more times to reduce the gland sufficiently.

In all operations for removal of a large or small part of the pancreas the great danger is in injury to the blood vessels in the region of the pancreas. Removal of the spleen may be necessary because of injury to the blood supply or to facilitate the removal of a growth.

The operation for hypoglycaemia and Whipple's operation for carcinoma of the pancreas have been the outstanding clinical advances in surgery of the pancreas in many years. Let us hope that within the next ten years the etiology, classification, diagnosis and treatment of pancreatitis can be put on a more definite basis than it is at the present time.

Thoracic Stomach with Short Esophagus and Diaphragmatic Hernia*

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"DIAPHRAGMATIC hernia" was the all inclusive term applied to a protrusion of the stomach through the diaphragm, until Bailey (1) introduced the name "thoracic stomach" to that type due to a shortening of the esophagus. There is a tendency to ascribe all of these lesions to a congenital, actual or potential defect in the diaphragm in contradistinction to the traumatic form of hernia through the diaphragm. A potential widening of the hiatus esophageus may, however, be a predisposing factor in the causation of the latter. In three patients of our series, an hiatus large enough to admit three fingers was found at the time that an operation was being performed for some other condition. Where formerly

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Fig. 1

diaphragamatic hernia was considered to be the more frequent lesion, it seems that the diagnosis of hiatus hernia and congenitally short esophagus is gaining in ascendency. An adherence to Akerlund's (2) classification of three types would help to clarify the situation immeasurably. There will be however, because of a lack of diagnostic methods, a large number of cases which will be unclassifiable.

Our interest in this subject was aroused by the fact that we were encountering these lesions in greater numbers, undoubtedly due to an increasing number of reports in the literature, and an increasing ability to recognize them. Therefore, when we decided to study this condition more thoroughly, we recalled as many of our patients as we could, in whom the diagnosis of "diaphragmatic hernia" had been made previously, with the purpose of trying to differentiate them into recognizable types. As we were only partially successful in our attempt, one of us enlisted the aid of esophagoscopy and later biopsic examination as suggested by Clerf and Manges (3). It is quite obvious that this kind of examination is superior to that of localizing the length of the esophagus by the level of the thoracic vertebra, although the latter is a much simpler procedure. Unfortunately we were unable to obtain the consent of all the previously examined patients to return for another fluoroscopy and still less for esophagoscopy. While we were thus enabled to increase our ability to differentiate the types, we did not acquire a corresponding increase in our facility to make a clinical diagnosis of the condition beforehand. On several occasions we suspected the lesion, only to find ourselves wrong in the majority of cases. We are inclined to agree with Ritvo (4) that in the majority of the cases it is an accidental finding without characteristic symptoms. The symptoms related by the patients are more frequently due to some other underlying cause. If more individuals were examined roentgenologically, the lesion would undoubtedly be found more frequently.

Incidence: Eleven patients were males and twenty-seven females. All of our cases were in adults. The ages ranged from 31 to 70. Only seven of these were in the seventh decade of life.

Symptoms: A restatement of the symptoms will be nothing new. We shall therefore make an analysis of the symptoms encountered in the hope of finding out which ones, singly or in combination, might suggest a diagnosis before other methods of investigation are utilized.

Twelve complained of epigastric pain, for periods varying from one to twenty-four years. In three of these the pain was worse at night, or on lying down, and in four it radiated to the left. One patient stated that the pain was distinctly worse on attempting to lift a heavy weight, Fig. 1. This patient, a woman of 51, was seen in 1933 because of pain in the right upper quadrant of the abdomen of eight years duration. She had some pyrosis which was relieved by soda bicarbonate, but no dysphagia. The gall bladder concentrated the dye normally. We mention this negative point because on X-ray examination a narrowing of the esophagus was found in addition to a large supradiaphragmatic gastric pouch. She came to the hospital for esophagoscopy and then changed her mind. This is probably a case of thoracic stomach on the basis of a congenitally short esophagus.

In the four patients whose pain radiated to the back, the lesion was of medium size in two, large in the second, and small in the third. In the last patient the esophagosopic length was 40 cm. and biopsic examination revealed esophageal tissue at that distance. The impression obtained, therefore, is that this might well be a case of para esophageal diaphragmatic hernia, which incidentally is the impression obtained on fluoroscopic examination. Another patient, female, age 51, with a medium sized gastric pouch had complained of severe pain in the left upper quadrant radiating to the back for many years—in fact as long as she could remember. The pain came on immediately after meals and was made worse by a heavy meal. Occasionally



Fig. 2

the pain occurred at night. The gall bladder concentrated the dye normally. The esophagoscopic length was 40 cm.

The mucosa at the cardiac orifice was reddened. Biopsic examination revealed gastric tissue. This is probably another case of para esophageal hernia. Three of these twelve patients had cholelithiasis.

"Heartburn" occurred in twenty-two patients, in seven of whom it was relieved by soda bicarbonate. In eight, it was definitely worse at night or occurred only on lying down, to be relieved when the patient assumed an upright position. In three of these the lesions were of medium size and associated with esophageal constriction above the gastric pouch in two. In one of these, a patient, age 56, who was afraid to lie down because of heartburn, esophagoscopy revealed an hyperemic mucosa which bled easily, and a thickening of the posterior folds at a level of 32 centimeters. In spite of this definite picture of esophagitis, her only complaint was nocturnal pyrosis without dysphagia. Another patient, a male, age 11, complained of heartburn for about eighteen years, when lying down. X-ray examination revealed a large gastric pouch with an esophageal constriction. The esophageal length was 37 centimeters. The diagnosis is probably thoracic stomach with short esophagus.

Six of these twenty patients had cholelithiasis. How much the pyrosis was due to this and how much to the gastric lesion, is difficult to tell. In the majority of cases there was no relationship between the size of the lesion and the amount of heartburn.

Vomiting, alone or with regurgitation, occurred in ten patients, and regurgitation in four. Relief of the distress by vomiting was not common. In five of these patients the lesion was small, in two large and one medium.

Pain in the chest, either of a substernal type or radiating to right or left, occurred in only 6 patients. One of these patients came to see us in 1931 complaining of irregular gastro-intestinal discomfort. Two years before, a diagnosis of chronic cholecystitis was made in Detroit by very capable physicians. At times the patient complained of severe right hypochondriac pain. About one year later he had severe pain in the left precordial region, radiating to the left shoulder and arm. The gall bladder concentrated the dye well and an electrocardiogram showed no deviations from normal. A tentative diagnosis of diaphragmatic hernia was recorded on the history, but it could not be confirmed by X-ray examination. Four years later the diagnosis of thoracic stomach and short esophagus was made at the Mt. Sinai Hospital, New York, while the patient was under the care of Dr. Winkelstein. Hurst (5) reported the case of a patient with recurrent hernia of the stomach through the hiatus esophageus of the diaphragm with pain resembling angina pectoris. Three patients in this group had dysphagia, but esophagoscopy was unsuccessful in two and not tried in one. One other patient in this group will be discussed later. In two it was undecided whether the pain was referred into the chest from calculous cholecystitis, or from the gastric pouch.

A history of dyspnea was obtained in six patients. In all of these the lesion was either of medium or large size. Goodall and Hoyt (6) lay great stress on dyspnea of a peculiar type which occurred in four of their five patients. They found a characteristic dyspnea, one occurring on the slightest effort or after eating—a sort



Fig. 3

of panting breathing—disappearing when the patient sits down and prone to be absent even on exertion, when the stomach is empty.

They divide their cases in two types—one in which the major part of the stomach is above the diaphragm, and the other in which the major part is below the diaphragm. The intense type of this remarkable form of dyspnea occurs in the first type and lead the authors to make a clinical diagnosis of thoracic stomach in two other patients, after having found a thoracic stomach on X-ray examination in the first patient who had this sort of breathing. We did not encounter this severe symptom in any of our patients because the lesions were all of the second type, with the exception of one who refused to come back for a re-examination. Six patients complained of some form of dyspnea. One in this series, Fig. 2, a woman of 38, complained of epigastric pain, nausea, vomiting, tightness and a smothering sensation of the chest with frequent attacks of dyspnea. She had stomach trouble dating back to childhood. In 1926 she was told that she had asthma. An X-ray examination revealed the largest thoracic stomach in our series. Unfortunately we lost track of her and could not get her back for re-examination or esophagoscopy. In the light of Goodall and Hoyt's report and the fact that her symptoms dated back to childhood, we are inclined to consider this case as one of congenitally short esophagus and thoracic stomach.

Dysphagia occurred in six patients. In the report of Clerf and Manges (2) dysphagia was a prominent symptom. Their patients differed from ours in that the majority came to them primarily for difficulty in swallowing. The lesions were of medium size in two, small in three, and undetermined in one. Two had indefinite chest pain and three heartburn at epigastric

pain. Esophagoscopy was carried out unsuccessfully in three patients.

They refused to return for re-examination. X-ray examination revealed a supragastric constriction. One of the patients ,Fig. 3, male, age 62, had difficulty in swallowing over a period of two years and had had repeated attacks of biliary colic. X-ray examination revealed a thoracic stomach with an esophageal narrowing and cholelithiasis. A cholecystectomy was done, at which time it was found that the hiatus esophageus admitted three fingers quite readily. The dysphagia returned later. Esophageal dilatation gave him some relief. Esophagoscopy was attempted, but because he violated instructions not to partake of fluid and denied having done so, it was unsuccessful as gastric fluid regurgitated into the esophagus at the time of examination. He refused to return for re-examination.

In attempting to *evaluate these symptoms*, we were confronted by the fact that many of the patients who had other pathological conditions, as calculous cholecystitis (11 cases), hypertension with or without cardiac involvement (8 cases), hyperthyroidism (2 cases) and syphilis (2 cases), had the same complaints as those patients with thoracic stomach without these lesions. It is, therefore, very difficult to determine upon a symptom complex which is typical of thoracic stomach. The following symptoms are suggestive: increased pain or heartburn on lying down, pain in the chest radiating to the left or down the left arm and dyspnea, neither one of cardiac origin, and difficulty in swallowing of long duration in a patient in whom traumatic stricture, carcinoma of the esophagus or cardiospasm can be ruled out.

X-ray examination: In every case the actual diagnosis was made by X-ray examination. Attempts to visualize both the hernial protrusion and the esophagus as suggested by Einhorn (7) were unsuccessful in most cases. It was necessary to give the patient some more barium and visualize both structures at the moment of the passing of the barium. This should be an excellent method for differentiation. Unfortunately a second meal of a thick paste was not always successful. We classified our lesions as small, about 3 centimeters or less in diameter, medium 4 to 6 centimeters, and large 7 centimeters or more. Fifteen were small, eleven medium and eight large.

X-ray examination alone sufficed to make a diagnosis of para esophageal hernia in seven patients, in one of whom it was confirmed by a double meal, and in six by finding the esophagus to be of normal length. In one patient dilatation of the esophagus by X-ray was found and esophagoscopy revealed shortening. In six patients the finding by X-ray of a constriction of the lower end of the esophagus with a supradiaphragmatic gastric pouch suggested the presence of a short esophagus. Only one of these was confirmed by esophagoscopy alone, as the other patients refused to return for further examination.

Esophagoscopy was employed for the purpose of getting information about the condition of the esophagus, determining its length and later to obtain specimens of tissue at the level at which gastric mucosa was seen. It is ordinarily accepted that the distance from the teeth to esophagus is 40 centimeters. However, this may vary some with the heighth of the patient. In this report 39 to 40 centimeters are accepted as normal, except in those patients in whom a constriction is found at the lower end of the esophagus, in addition to roentgenological evidence of a supradiaphragmatic pouch of the stomach. Because of our inability to have all patients with this possibility return for esophagoscopy, we are unable to furnish any definite statistics on this point. Esophagoscopy was carried out in fifteen patients. In nine it was responsible for the diagnosis, and in six it confirmed the diagnosis made by X-ray.

The results of *biopsic study* in nine patients showed that gastric mucosa was obtained in three patients at a level where the esophagus should be, and esophageal mucosa in the others. Because of a constriction at the lower end of the esophagus in three cases, it was impossible to enter the stomach. X-ray examination, however, revealed the fact that the esophagus was constricted above a small protrusion of the stomach above the diaphragm. In some patients in whom the esophagoscope was passed to the 39 or 40 centimeter mark, there is still the possibility of the lesion being a paraesophageal hernia—that is, a real diaphragmatic hernia. Many more studies will be necessary to determine this fact. In all cases where a biopsy was made, the esophagoscopic diagnosis was confirmed. It seems unlikely that this method of examination is necessary except in extremely doubtful cases.

SUMMARY AND CONCLUSIONS

1. Thirty-nine patients were seen with the diagnosis of some type of thoracic stomach. In 7 the lesion was a paraesophageal hernia. This diagnosis was confirmed by X-ray examination and finding the esophagus to be of normal length. In one it was confirmed at fluoroscopy by a double meal. Many may question the frequency of this lesion, and rightly so, because of the tendency to consider most of them to be due to congenital shortening of the esophagus.

2. In nineteen the diagnosis was thoracic stomach due to a shortened esophagus. In six a constriction of the esophagus above the gastric pouch was seen. In 9 the diagnosis of short esophagus was made or confirmed by esophagoscopy. In one the history of difficulty in swallowing and finding a constricted esophagus by fluoroscopy, and in another the history of gastric disturbance from childhood on, without an esophageal constriction, were sufficient to make the diagnosis. In one patient the diagnosis was made elsewhere. In 12 it was impossible to determine the kind of lesion found.

3. A clinical diagnosis of thoracic stomach should be suspected in patients presenting the above mentioned symptoms over a long period of time, in whom other pathological conditions can be ruled out.

4. The thoracic stomach of unknown type requires more careful examination by various methods, as X-ray, double meal and esophagoscopy for differentiation.

5. Biopsy is only a confirmatory procedure and is unnecessary where esophagoscopy is satisfactory.

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DISCUSSION

DR. JOHN H. FITZGIBBON (Portland, Oregon): Dr. Bloch did not mention bleeding as a complication of diaphragmatic hernia. I have seen over thirty cases, out of which group two patients have had severe hemorrhages and a history suggestive of peptic ulcer, but with no X-ray evidence of abnormality other than hiatal hernia. It is reasonable to assume that they were bleeding from ulceration in the herniated part of the stomach. Both responded well to ulcer management and are continuing treatment. The recurrence of ulceration without hemorrhage in these patients is something that should be given serious consideration. If stools are routinely examined, we shall find occult blood continuing over long periods in many. Secondary anemia is occasionally an outstanding feature.

Dr. Bloch's paper brings out the fact that hiatal hernia is rather common, and I feel that we should emphasize the importance of horizontal fluoroscopy. No gastro-intestinal X-ray examination is complete unless the patient is examined lying flat or with the head lowered. Upon taking a deep breath and straining, barium will be seen to "pop" up through the hiatus into the hernia. If this sort of examination is made routinely, particularly in people who have been suspected of having gall bladder disease or who have been operated upon for supposed gall bladder symptoms without subsequent relief, hiatal hernia will be found much more commonly than is generally realized.

DR. RALPH C. BROWN (Chicago, Illinois): Adding to what Dr. Fitzgibbon has said, I am convinced that peptic ulcer occurs in association with these hiatus herniae, possibly resulting from the ischaemia produced in the mucosa of the stomach at the point of constriction. I have seen massive hemorrhage in association with at least one such case, and in two other cases there was such a degree of perigastritis at the point of constriction of the stomach as to involve the esophagus in scar-tissue to such a degree as to produce obstruction which required dilatation.

I think the probable association of peptic ulcer with hiatus hernia is something which at least should be kept definitely in mind. It is difficult to see the ulcer lesion when it exists at the point of constriction, so I am not able to state with absolute certainty that peptic ulcer occurred in the three cases to which I have referred. However, all three of these cases responded immediately and permanently to the therapeutic test of routine ulcer management.

DR. JOHN L. KANTOR (New York City): In addition to frank hemorrhage, there may be oozing in cases of diaphragmatic hernia. This is one of the causes of obscure anemia that should be kept in mind.

There was one case of this kind in New York that masqueraded as carcinoma. It was discovered by the late Dr. Rothschild, an internist. It is well worth knowing that by examining these people in the ordinary erect position and giving them a Sedlitz powder, one may bring out a second shadow parallelling the diaphragm but higher up in the chest. This shadow represents the gas filled intra-thoracic portion of the stomach. The procedure was devised by Dr. Ball and published in the *J. A. M. A.*, October 19, 1935.

DR. LEON BLOCH (closing the discussion): None of these patients had an apparent hemorrhage, but one had a definite ulcer which we could see with the esophagoscope very distinctly and bleeding had occurred. In all of the patients in whom esophagitis was found by the esophagoscope there was no question about the diagnosis: the mucosa was red, hyperemic, spongy and bled very readily so that undoubtedly had we examined the stool we might have found blood.

In two of the patients we found not only esophagitis but gastritis extending below the esophageal gastric margin.

The method of examination, of course, is important. All of the patients were examined, either lying down or in the Trendelenburg position. In most cases it is a simple matter to examine the patient in either the right or left oblique, or in the supine position. There was no difficulty in finding the lesion. Once in awhile we were aided in finding the lesion by having the patient take a deep breath, because when the diaphragm descended the gastric pouch came up very distinctly.

Specific Food Sensitiveness*

By

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IN the time available I can report only briefly on some of the impressions that stand out strongly from the experience of the last few years. First, I would like to say that there is no question in my mind about the need for the development of a greater interest in specific food sensitiveness on the part of gastro-enterologists and, for that matter, of physicians practising in every field of medicine. We should all of us be grateful to the allergists for having opened our eyes to the possibility of relieving several distressing syndromes, such as migraine and mucous colitis, by the forbidding of certain foods.

Dietitians also could profit from conversion to the view that the *digestibility* of a food may at times be much more important to a patient than is its content of vitamins or calcium or iron. So far, most of the books on dietetics either ignore the subject of digestibility or else dismiss it with a few words, and the individual dietitian, unless she has been specially trained under an allergist, is likely to have little patience with anyone who claims that he cannot take milk or eggs or spinach or orange juice. Time and again highly allergic patients have told me of the miserable experiences they have had in hospitals where, after an operation, they were forced to continue eating the so-called "health foods" long after the prophesied vomiting or painful bloating appeared.

Perhaps I should say that the outset that I have no intention of joining the group of enthusiasts who seem to believe that nearly every disease is due to food allergy. Perhaps when I have learned more about this subject my percentage of miracles and cures will be higher, but as yet I must admit that I meet with far

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more failures and disappointments than with successes. In many cases I haven't even the desire to start experimenting with diet because the history suggests so strongly that the troubles are not due to the nature of the food eaten. This is particularly true when short spells of discomfort alternate with intervals of weeks or months when the patient is able to digest anything. In such circumstances, if the inciting factor were a food it would have to be one seldom eaten, and in such circumstances the patient would probably have recognized his idiosyncrasy. Or a woman with migraine will tell me that her headache comes only with menstruation or when she overworks or sits up late waiting to scold a wayward son, or when she takes a long automobile ride.

To be sure, in some of these cases migraine or vasomotor rhinitis may come as the result of the combined action of two insults, and the removal of wheat or some other food from the diet may enable the brain or the nose to withstand the effects of fatigue or menstruation or dust. Especially when, in a given case, facts in the history have warned the physician that the symptoms are probably not due to food, he will feel disinclined to keep on experimenting with narrow elimination diets unless they soon show definite signs of bringing relief.

Although, as I have said, I meet with more disappointments than miracles, when the miracles come they are so delightful that I feel that we physicians all owe it to our patients, to our reputations and to the good name of scientific medicine to keep constantly on the watch for cases in which remarkable successes can be attained.

Perhaps it would help if I were to stop for a moment to recount briefly three or four of the experiences which have convinced me that even those of us who are much interested in food sensitiveness must still be failing to recognize cases of the disease and must be turning away patients whom we could easily cure.

Thus, a few months ago, I saw with Doctor Rozendaal a young man who said that he was well until about seven years before, when he was a sophomore in college. He then began to have so much flatulence, abdominal pain, and mental cloudiness that study became almost impossible and he had to go home. There, in spite of treatment by many physicians, he continued to suffer so much that he could seldom do any work. My impression from looking at the man and listening to his story was that his mental deterioration was his part of a poor nervous inheritance which had produced a syndrome suggesting mild epilepsy in a brother, and I had no hope of helping him. All laboratory and roentgenologic reports were negative. It was only a forlorn hope that led us to experiment to see if an elimination diet would affect the abdominal distress. To our astonishment, he returned in forty-eight hours a different person. For years dull, apathetic and discouraged, he now was bright and wide awake, his ambition had returned, his head had become clear, his abdominal discomfort had disappeared, and he had begun to eat and to gain in weight. Soon he was able to work all day on his father's farm, and after a few months he wrote to say that his health was good so long as he avoided certain foods.

A physician was seen for several years with severe hunger pain, so typical of ulcer that it never occurred to me or to any of my colleagues to suggest a study of food sensitiveness. At times the pain was so severe that milk had to be taken every hour. Eventually the abdomen was explored, an ulcer could not be found, and pyloroplasty failed to give relief. In February, 1935, after an attack of asthma, skin tests were made and a tremendous sensitiveness to milk was discovered. Removal of this food from the diet brought immediate relief, and later it was found that orange juice and chocolate also had to be avoided. Since these three offending foods have been excluded from the diet, the patient has been perfectly well. I have seen now several such cases in which a desperate effort was being made to cure hunger pain with the very thing which was causing it; namely, milk!

For several years a man kept coming to The Mayo Clinic complaining of a sort of narcolepsy severe enough to cause him to fall asleep at the wheel of his car or while talking business in his office. All attempts at treatment had failed. Last year, when careful questioning revealed the fact that most of his trouble followed breakfast, I suggested that he go without this meal and then, if that helped, he could test one food at a time until an offender was found. I had little hope that he would find a cure this way and I had forgotten all about the man when, some months later, his home physician wrote that the avoidance of cream had worked a complete cure.

This brings me to another point that still deserves much emphasis, which is that *hurtful foods so often injure or irritate the brain.* To my surprise, once, while trying to cure hives in a man who had not worked for years on account of distressing feelings in his head, I accidentally cured the "insanity" and the man went back to take charge of his business again. On another occasion I saw a man in *status epilepticus* which was due apparently to his having gorged himself on strawberries, and I have seen people who knew that they would develop a vile temper if they ate certain foods. We all know that nightmares can follow the eating of a "Welsh rabbit," we know that splitting headache or migraine can follow the eating of chocolate or cheese, and I happen to know from personal experience that the eating of chicken or eggs can give rise to weird visions, annoying dopiness and even signs of meningeal irritation.

Besides the few cases in which a cure comes as a welcome surprise, there are, of course, the many in which it is to be expected because the patient has already learned that one or more foods will produce the symptoms complained of; he continues to suffer only because neither he nor his physician knows how to go about the business of discovering all of the noxious agents. If he is intelligent, all he needs to start him on the road to recovery is a little instruction in home detective work.

Obviously we cannot afford to waste time hunting for food sensitiveness in every patient, so the next question is: in what type of case should we be particularly careful to look for it? My impression now is that *we should look carefully for food sensitiveness* whenever the symptoms of abdominal distress point to the presence of an overly-sensitive colon, or when they are vague or unusual, or whenever careful examination fails to reveal any sign of disease in duodenum, stomach, gall bladder or appendix. We must study the diet in every case of true flatulence or bloating, and

we must look for food sensitiveness in some cases of migraine.

I doubt if it pays to study diet in every case of *migraine* because so often the history tells us that we are not likely to get anywhere along these lines. The headache may come only when the woman is menstruating or when she is very tired or has had an emotional debauch; or we may see at a glance that we are dealing with a psychopathic or markedly asthenic person or one whose brain has been made so irritable by overwork, worry, grief or pain that the little "explosion" that causes the attack can take place every few days without the help of any extra insult, such as can be derived from food. This type of case is so common that I doubt if any large percentage of people with migraine can be relieved by dieting alone.

Occasionally I can help a person with vasomotor rhinitis, but there are many more whom I do not help, again apparently because the sympathetic nervous system is so irritable and erratic that it can cause trouble without the help of irritants coming from without the body. Similarly I have had almost no luck in helping patients with the severe and almost constant type of urticaria. Often it seems to be brought out by worry and mental strain. I have had some luck in treating canker sores in the mouth; in one case, after a life-time of suffering, relief came when chocolate was removed from the diet. As I have already pointed out, we physicians must always be on the watch for patients whose feelings of autointoxication may perhaps be cured by dieting. It sems probable also that in some cases constipation is due to the irritation of the colon by certain foods, and in some, the symptoms of cholecystitis, ulcer or appendicitis can be imitated with great fidelity.

I should like to emphasize the point that it does not seem logical to assume that most of the annoyances that follow the eating of particular foods are allergic in origin and due to protein. I feel sure that there must be a number of drug-like substances in certain foods which can upset the digestive tract in much the same way as it might be upset if a person were to take a small dose of an emetic or a purgative. Instead of frank vomiting, there is regurgitation, belching, heartburn, and discomfort about the cardia, and instead of purgation there is peristaltic unrest and colicky pain.

Whether or not one accepts the view that food sensitiveness is usually due to the protein in the food, I cannot see why one should make strenuous efforts to purify the allergens used for skin testing. I should expect to get the best results with antigens obtained by the simplest treatment of the foods.

Another point that I would like to stress is that it is neither logical nor necessary to keep a patient on a narrow elimination diet for weeks or months as some physicians are doing at the present time. It seems to me that if good results are not secured in two or three days, one of two things is probable: either the diet still contains an offending substance or else the cause of the symptoms is not to be found in food. Rarely have I seen any good come from the continued use of an elimination diet that did not bring relief in forty-eight hours. This is to be expected from the fact that when a person eats some harmful food the symptoms generally appear within a few hours. Accordingly, when a patient returns after having been for forty-eight hours on a narrow elimination diet and says that he is no better, the physician must not ask him to keep on for a month but must face the situation immediately. He must either accept defeat and tell the patient to return to his usual habits of eating, or else he must continue experimenting with substitutes in the elimination diet. If this does not help the patient can fast for a few days.

Ordinarily I start patients on a diet of lamb, rice, butter, sugar, and canned pears. If after a few days their distress persists, I may leave them for two days on nothing but maple sugar, or I may ask them to fast. If after this they still have their distress, I lose faith in my ability to help them with diet. Rowe tells me that sometimes in cases of wheat sensitiveness it takes ten days or a month to get the offending protein out of the system, but if it took me that long to help a patient with diet, I would suspect that the relief that came was due to some other factor such as rest, unconscious psychotherapy, or a spontaneous remission of symptoms.

Even when the elimination diet fails to help, it often gives much valuable and even decisive information as to the nature of the patient's troubles. Particularly in the case of women, one can learn so much from the way in which an individual faces or fails to face the little annoyances associated with the dieting. Often she frets so much, she acts so unreasonably, and she shows herself so irritable and so lacking in backbone and good sense that the diagnosis of "Fox's disease" can promptly be made. For those who are not acquired with Fox's disease I will say that, one morning, a chief asked his interne, named Fox, what he thought was the matter with a certain woman whose case he had just been working up. The answer was, "Well, doctor, it looks to me as if she were just a plain damn fool!" The chief was so entirely satisfied with this diagnosis that thereafter, in that hospital, the particular syndrome was known as Fox's disease.

Another point that has been impressed on me time and again in the last few years is that commonly the skin tests not only fail to help the physician in his search for offending foods, but sometimes the obtaining of a few positive results is actually a nuisance because both the patient and his physicians put such a blind and unswerving faith in them. In many cases it is almost impossible to get the patient to touch the incriminated foods again. I have spent hours trying to get these people to see that the reaction of the skin may or may not have supplied a trustworthy hint. In every case one should proceed with the experiment of eating the suspected food to see if this makes the symptoms any worse, or of avoiding the food to see if this brings relief. Surely no food should be banned forever simply because the skin once reacted to it. Sometimes when the tests are repeated the skin is found to respond to a different set of foods.

The difficulty is that we human beings are all a bit lazy; we dislike thinking and reasoning, and hence whenever possible we cling to a laboratory diagnosis which we hope will save us from having to work one out for ourselves.

SUMMARY AND CONCLUSIONS

To sum up, then, although there are more disappointments than miracles in the search for and the curing of severe manifestations of food sensitiveness, the miracles are so gratifying when they come that, each time, the clinician will resolve to spend more time looking for them. The field is still much neglected;

more diets must be fitted and fewer handed out ready made.

A good history will often show that the diet is probably not the cause for the patient's discomfort. Patients must not be left too long on narrow elimination diets; such diets are for testing and not for treatment.

Some cases of diarrhea and pseudo-ulcer are due to the milk that is taken by way of treatment, and not infrequently certain foods irritate or greatly depress the brain. Somnolence after meals can be due to a particular food, and canker sores in the mouth can be produced by food.

Efforts to use an elimination diet are often instructive in showing the physician that he is dealing with an unreasonable, overly fussy, querulous, or psychopathic person.

Food sensitiveness is not necessarily allergic or due to protein. Perhaps partly for this reason, skin tests are of little help in finding the foods that cause indigestion.

DISCUSSION

DR. ARTHUR F. COCA (Pearl River, New York): Food sensitivity is limited to the group of familial or atopic allergy in which are associated hay fever, asthma, the urticaria due to foods, atopic dermatitis, gastro-intestinal allergy, migraine and others.

In the typical case (such as hay fever) antibodies—those peculiar atopic antibodies of the human being—are regularly demonstrable in the blood and indirectly through the positive skin test. The positive skin test appears only when these antibodies are present in the blood. They are often entirely absent, for some reason that we do not understand; in such cases the skin test results negatively.

Food sensitivity can be at the bottom of any of these many clinical varieties. Some of them are associated with a positive skin reactivity and others not. If the clinical form of the food sensitivity is asthma or hay fever, or atopic dermatitis, the skin test is quite regularly positive.

I have included atopic dermatitis (neurodermite) among the clinical varieties of food sensitivity in which the skin test is frequently positive. This statement must be considerably qualified by the further remark that the direct skin reaction in this condition is almost always so weak that it cannot be used diagnostically. However, a means has been developed by Matthew Walzer in Brooklyn of magnifying this weak reaction in a way to make it a thoroughly practical and reliable specific test. This means is the indirect test, which is performed with the technic of Prausnitz and Kuestner. The test is carried out as follows:

Serum is obtained from 5 to 10 c.c. of the blood of the patient by aseptic defibrination and centrifugation. One-twentieth c.c. of the serum is injected intracutaneously in about 50 well-separated sites in the upper arm of a substitute, who must not be allergic. Three days later these injected sites can be tested with the intracutaneous method with the usual food extracts, an identical control injection being made in a normal skin site in the same skin. In comparison with the negative result of the control test, slight degrees of reaction can be recognized as diagnostic which could not be accepted as significant in the direct test in the patient's skin.

By this means, Dr. Walzer states, about 60 per cent of subjects of neurodermite can be relieved by the avoidance of the indicated foods.

Notwithstanding the valuable contribution of Dr. Walzer to the technic of skin tests in the development of his indirect test, it still remains true, as Dr. Alvarez says, that in many cases of food sensitivity, especially urticaria, allergic headache and gastro-intestinal allergy, the skin test is of very little use. It is in such skin-negative cases that the physician must fall back on the trial diet plan.

The trial diet plan can succeed only if we possess a criterion of reactions, like the wheal in the skin test, that is diagnostically significant. The criteria under the trial diet plan are, of course, the clinical symptoms of food sensitivity. Such symptoms may be immediate or delayed. Immediate symptoms are gastric pain, headache (which may occur within a hour after the ingestion of the offending food), swelling of the lips in some instances, and a peculiar sensation of the mucous membrane of the tongue, which can be very acute. Vomiting is seen in some cases. The more violent symptoms should be avoided, if possible, by administering at the first trial only a small quantity of the food to be tested, where such symptoms are feared.

I have for some time been making use of another immediate symptom which seems heretofore to have been overlooked. This is tachycardia. I do not know how often this appears. It happened to be prominent in the first four cases of food allergy that I have had occasion to study. The symptoms in all these cases were gastro-intestinal or migraine. The tachycardia can range from a rate of 80 or 90, lasting for some hours after the ingestion of the offending food. In one case that had recently suffered a coronary thrombosis, the pulse rate has risen to 160 or 180 or more within a half hour after the injection of minute quantities of the offending substance. Three of these cases could be completely relieved of their symptoms by elimination of foods through the use of the criterion of tachycardia.

Delayed symptoms are more difficult to use as criteria of reactions. These are urticaria, diarrhea, bleeding from the intestinal tract. (This latter symptom may be more frequent than is generally known because patients are not advised to examine the stool for gross evidences of bleeding). Dizziness is a delayed symptom; also extrasystole, which may be the sole symptom of food allergy in some cases. A feeling of lassitude is a distinct delayed symptom in some cases.

In the application of the trial diet principle, all plans heretofore recommended have exhibited a common error which may explain some, at least, of the many failures encountered in the use of this principle. This mistake is the illogical one of trying more than one food at a time. Different allergists recommend different combinations of food in the initial test. The successes under all these plans represent merely those lucky individuals who happened to be sensitive to relatively few foods which were not included in the first selection.

Another circumstance which has no doubt interfered with the successful application of the trial diet principle is the fact that there are allergenic foods which have not been recognized as such by even the allergists. Among these may be mentioned gelatin, which, according to the chemists, contains no native protein but which, nevertheless, can be a violent food allergen. Another allergenic food that has been largely overlooked is sugar, both from cane and from beet. There is relatively very little protein in sugar. When the protein is collected out of a solution of sugar by the process of ultrafiltration, it is found that there is something over 100 milligrams of it in 200 pounds. On the basis of the established fact that about 1 per cent of negative protein in solution will find its way through an ultrafilter when the ultrafiltration has proceeded for a period of about 48 hours, I have been able to calculate that 1/100,000 of a milligram, or possibly less, of sugar protein may cause disagreeable allergic symptoms (tachycardia, dizziness and headache) when that quantity is given daily over a period of two days.

The logical plan of applying the trial diet principle must be, first, to withhold all food until the symptoms disappear and, secondly, to administer one food at a time in ample quantity, each food being added only after the preceding

but which in reality probably represents a small acute transient process in the course of the slowly progressing degenerative, sclerotic or infectious process which is called "chronic pancreatitis."

As regards treatment, pancreatic ferments by mouth, the minimizing of infection elsewhere and the proper diet, especially one limited as to fats, unquestionably help certain of these cases. I have always felt in this connection, that it is probable that in certain cases of cholecystitis, with or without stones, the benefit that follows from a fat low or fat free diet is not all due to its effect upon the biliary infection, but is rather due to the effect of this diet upon the associated pancreatic disease or dysfunction so frequently associated with gall bladder disease. In my experience, if gall bladder disease, even cholelithiasis, is not associated with jaundice or pancreatic trouble, the simpler fats, butter, cream, olive oil and especially egg yolk are in reality our most valuable dietetic aids in promating gall bladder drainage and should be used in large amounts.

Are there *functional disturbances* of the pancreatic external secretion? There must be, for the pancreas is supplied with autonomic nerves which unquestionably play some, if not the major, *rôle* in stimulating or inhibiting secretory activity and therefore there certainly must be examples of hypo-, hyper-, and achylia-pancreatica of this origin. But its diagnosis is obviously extremely difficult; probably in most cases impossible, for while we may suspect it, it is very hard to differentiate from mild chronic pancreatitis, just as it is equally difficult or impossible to differentiate certain functional gastric disturbances from a mild gastritis, although the gastroscope may settle this question.

I have seen a few cases, however, in which I think the diagnosis was absolutely justified. Let me report one—a woman who had been operated upon many years ago and eighteen gall stones removed from the gall bladder. When seen by me fourteen years later, she had definite recurrent gall stones attacks and I had her operated upon with a removal of the gall bladder filled with stones. The pancreas was found perfectly normal at the time but a few days after the operation she developed an intractable diarrhea with typical butter stool and complete absence of pancreatic diastase and trypsin. Time, diet, possibly helped by the administration of pancreatic extract in large amounts, cleared up the condition; in a relatively short period of time, the diarrhea stopped, the stool regained its normal character. That the pancreatic trouble was purely functional, I think was shown beyond question not only by the rapid return to normal of the stool and the reappearance of pancreatic ferments in the fecal material, but by the fact that in a subsequent operation made about three months later for adhesions, the pancreas was examined carefully and found to be just as normal as it had been at the time of the preceding operation. If diarrhea follows cholecystectomy, as it does in a very small proportion of cases, it is probably often of this origin.

In thinking over the problems of the pancreas, one cannot fail to ask himself certain questions not answered in this rapid survey of our experience in this field. The most important is—is the pancreas an absolutely essential organ? Apparently not as regards its external secretion for proteolysis can be brought about by the pepsin and hydrochloric acid of the stomach, the erepsin, and possibly other ferments of the small intestine, and possibly by bacterial action. There is diastase from the salivary glands with minimal amounts from Brunner's glands and the bile to carry on starch digestion. The fats, however, will fare rather badly for lipase is derived almost exclusively from this organ and fat digestion is practically always impaired in extensive pancreatic disease or dysfunction. But, after all, good health may be maintained on a high carbohydrate, high vitamin, normal protein, low fat diet.

There is clinical as well as experimental evidence that the pancreas is not absolutely essential. Functional pancreatic achylia with its butter stool, if treated with the proper diet, does not seriously affect the general health. Even in organic conditions where there is complete absence of this secretion, such as in a few cases of tropical sprue, a certain number of cases of cirrhosis and many cases of carcinoma of the head of the pancreas, death does not come early but at long last. Certainly in cases of carcinoma of the pancreatic head, the symptoms in the early stages—malaise, depression, pruritus, chills and fever, even pain—are not due to the cancer *per se* but are symptoms of a progressive jaundice with biliary toxemia. Thus the marvelous temporary improvement after cholecyst -gastrostomy or -duodenostomy! There is experimental evidence also in favor of this. For instance, in 1912, in a series of experiments made upon dogs with pancreatic fistulas, we found that as long as they were given plenty of fluids and plenty of alkali, their condition remained extremely good for a long period of time. If, on the other hand, the common biliary duct was subsequently ligated and a complete obstructive jaundice produced, in every case this was followed immediately by rapid loss in weight and strength and early death, emphasizing anew the great importance of the bile as a partial substitute for the pancreatic secretion if the latter is absent or markedly diminished.

These findings — clinical and experimental — are really of great significance for they justify partial or complete pancreatectomy for carcinoma. The salivary, gastric and intestinal secretion, and bile, possibly helped by pancreatin by mouth, will act as substitutes for the external secretion; insulin, possibly some day, pancreas transplantation, for the internal secretion.

Is pancreatic disease more common than is supposed or diagnosed? I am sure so. Can it be recognized or suspected more frequently than at present? I believe so, if one but keeps in mind its possibility in all cases with vague upper abdominal symptoms, with and without pain, and then utilizes all possible diagnostic procedures.

Perhaps there is no better way to end this fragmentary talk on the clinical aspects of pancreatic disease than to repeat what was said by Sir Archibold Garrod many years ago—"The chief difficulty in diagnosing disease of the pancreas is in thinking of the pancreas."

Surgical Aspects of Diseases of the Pancreas*

By

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IN a paper read before the New England Surgical Society in September, 1921, on "Acute Pancreatitis," I said that the term would probably always be used but that I would try to show that it was not descriptive enough and that the terms *acute pancreatic necrosis* or *acute hemorrhagic necrosis of the pancreas*, and *acute and chronic interstitial pancreatitis* would describe the various conditions found more accurately. I can find no reason for changing this opinion in spite of the fact that no one seems to have followed my suggestion.

Archibald (Lewis' "Practice of Surgery") has helped matters very much by dividing pancreatic cases into six groups, as follows:

(1) *Hyperacute pancreatic necrosis.*
(2) *Acute pancreatic necrosis.*
(3) *Subacute pancreatic necrosis.*
(4) *Acute pancreatic oedema.* (Zoepffel)
(5) *Chronic pancreatitis with recurrent subacute attacks.*
(6) *Chronic pancreatitis with sclerosis* (following acute attacks).

So far as dividing these cases into definite groups is concerned, this classification is of value, and if it were properly used we should not have such variation in the mortality statistics under the heading of acute pancreatitis as we have at present, when it varies from 22.7 per cent to 70 per cent or more. This great variation in mortality must be due to the variation in the type of cases used rather than to the difference in the skill of various surgeons.

My objection to this classification is that I believe there are two types of pancreatitis:

(1) Acute pancreatic necrosis, due to injury to the pancreatic ducts by retrojection of bile or duodenal contents into the pancreatic ducts, causing a digestion of the pancreatic parenchyma.

(2) An infiltration of the interstitial tissue with enlargement and an increased hardness and at times oedema. The condition may be either acute or chronic. The parenchyma of the gland is not involved. This should be known as interstitial pancreatitis.

With an idea in my own mind that the classification, etiology, pathology, symptomatology, and treatment of pancreatitis had been clarified to some extent, I was much disturbed to find that there was more confusion than ever about these points. It is impossible to discuss these cases until we can at least agree upon some classification, and classification cannot be agreed upon until the pathology has been agreed upon. Archibald has classified the cases of pancreatic necrosis, but what constitutes a pancreatitic necrosis? I have classified as pancreatic necrosis any case of pancreatitis in which there is fat necrosis or hemorrhage, because it is my belief that neither occurs without the release of activated pancreatic secretion which in turn causes pain and tenderness in the upper abdomen with nausea.

Archibald has a group which he calls chronic pancreatitis, which is due apparently either to very mild repeated attacks of pancreatic necrosis or to repeated attacks caused by the backing up of nearly normal bile into the pancreatic ducts, which he calls "subacute attacks of pancreatitis." He has still another group which he calls chronic pancreatitis with sclerosis, due to acute attacks of pancreatic necrosis, I assume, as only a necrosis could cause the amount of destruction he speaks of.

It has been my contention that there is an interstitial pancreatitis without involvement of the parenchyma, due to infection of the interstitial tissue. There are many cases of so-called interstitial pancreatitis of which there are no symptoms at any time, unless an abscess is formed and that seldom occurs. It is found only during the course of operation for other causes, such as cholelithiasis, peptic ulcer, or abdominal infection.

Three articles have been published recently in which various pathological changes have been classified under chronic pancreatitis and chronic interstitial or interlobular pancreatitis. Hinton (Annals of Surgery, September, 1932) states that duodenal and gastric ulcers in contact with the pancreas cause interlobular pancreatitis, which causes severe pain relieved at once by gastro-enterostomy. DeTarnowsky and Sarma (Annals of Surgery, June, 1935) describe *chronic pancreatitis* as a thickening of the gland due to repeated attacks of acute subsiding pancreatitis. Elman (Surgery, Gynecology, and Obstetrics, Nov., 1935) confuses the matter still more by reporting six cases of chronic *interlobular* pancreatitis, three of which had fat necrosis and three of which had no fat necrosis but had gall stones.

Under such conditions how is it possible to discuss chronic interstitial pancreatitis intelligently? I can only say that I myself have never seen a case of "chronic interstitial pancreatitis" without hemorrhage or fat necrosis diagnosticated before operation. Such conditions have no symptoms so far as I can determine.

The *mortality* of the two groups, acute pancreatic necrosis and chronic interstitial pancreatitis, is strikingly different. There is a mortality of at least 50 per cent in the cases in which the parenchyma is involved, while in the second group the mortality cannot be more than 2 to 3 per cent. If we accept Archibald's classification of acute pancreatic oedema (Zoepffel) as an acute interstitial pancreatitis, this would bring up the mortality rate somewhat. If, however, it is classed as acute pancreatic necrosis, as I believe it should be, the mortality rate corresponds accurately to the mortality rate of the acute pancreatic necrosis group.

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Not only are these two groups different in pathology, etiology, and mortality, but the two have entirely different symptoms. In the first group the patients are always operated upon because of symptoms due to the pancreatic necrosis or retrojection of nearly normal bile, while in the interstitial pancreatitis group they are operated upon because of symptoms due to biliary disease, duodenal or gastric ulcer (Hinton), or abdominal infections.

If we accept the division of these cases into the two groups, (1) acute and chronic pancreatitis due to activated pancreatic secretion or nearly normal bile, and (2) interstitial pancreatitis probably due to infection of the pancreas, and accept Archibald's division of the pancreatic necrosis cases into four groups, we can talk about the operative procedures and mortality of each.

There is some difference of opinion in regard to the type of operation to be performed. Archibald believes it necessary only to drain the biliary system. This appears logical, but what of the four autopsies reported by Opie some twenty-five years ago, in which the necrosis was limited to the area drained by the duct of Santorini which opened separately into the duodenum. While it is logical to drain the biliary system, there are undoubtedly a certain percentage of pancreatic necrosis cases due to retrojection of bile into the duct of Santorini. In fact, Opie states that the duct of Santorini is the main duct in 10 out of 100 autopsies.

The operative procedures for the various divisions of Archibald's classification should be settled in the minds of all surgeons. The extent of the operation should be determined by the condition of the patient. The very sick should have the least possible done; that is, drainage of the fatty capsule. If the surgeon believes it reasonable, a cholecystostomy with or without removal of stones may be done. Those in slightly better condition should have the fatty capsule and the true capsule, where soft areas are found, drained and a cholecystostomy done with removal of gall stones. In those patients in still better condition the gall bladder should be removed, the ducts explored, and a choledochostomy done.

It is self evident that drainage of the common duct will give freer flow than will drainage through the gall bladder, but it is necessary not infrequently to do a cholecystostomy because of the condition of the patient or because of the difficulty of reaching the duct.

Archibald does not approve of cholecystectomies for fear that the gall bladder may be needed for drainage later, but the great majority of surgeons do remove the gall bladder if the condition of the patient will permit it.

It is difficult to see the objection to drainage of the fatty capsule when it is infiltrated and tense and contains much broken down tissue. While I agree with Archibald in practically all of his work, I cannot agree that drainage of the biliary system is all that is necessary. I feel strongly that drainage of the fatty capsule, and the true capsule of the gland so far as it can be done without injury to the pancreas, is of great advantage to the patient. I have seen many patients relieved of pain and shock after drainage of the fatty capsule, and have had two very definite cases in which the patient remained uncomfortable, nauseated, and unable to eat after biliary drainage without drainage of the fatty capsule. Both were comparatively mild cases and both recovered after ten days which were very trying both to the patient and to the surgeon. I have never since neglected to drain the fatty capsule when there is swelling in the region of the pancreas, fat necrosis, or hemorrhage, no matter how slight.

It is true that drainage of the fatty capsule is more likely to cause an infection of the fat about the capsule than no drainage, but on the other hand proper drainage at the primary operation may prevent a secondary operation for the drainage of an abscess in this region. The neglect of early drainage of abscesses may, I believe, be responsible for some of the late deaths. When the fatty capsule is drained early, the patient frequently runs a moderate temperature or none at all for a week or ten days, at the end of which time the temperature rises to 101° or 103° with increased discharge of pus, broken down fat, and necrotic gland. A secondary operation is frequently necessary to give better drainage unless a large drainage wound is left at the first operation.

In addition to the difficulties of post operative drainage of the fatty capsule, these conditions not infrequently cause thrombosis of the veins in this region, not only the splenic vein but even the vena cava. The sepsis which is often present may cause infection in other regions, the same as any abdominal infection.

There have been changes in the minds of some surgeons recently in regard to the best time for operating on cases of acute pancreatic necrosis, largely because of the high mortality in these cases with our present method of so-called "early" operation. But are there enough cases operated upon within twenty-four hours to give us a proper idea as to the value of early operation? At the Massachusetts General Hospital early operation has largely been given up.

DeTakats and MacKenzie (Annals of Surgery, September, 1932) believe that:

(1) "Patients should never be operated upon in the initial shock," and yet their statistics show that the mortality in those cases operated upon within 24 hours is 25 per cent, the lowest mortality except for the group operated upon more than three weeks after the onset of symptoms. It may not be proper to operate within 2 to 6 hours after the onset, but it is a well known fact in surgery that removal of any condition causing shock will frequently save the life of the patient. The surgery must, of course, be reduced to a minimum. It is my belief, therefore, that all cases of pancreatic necrosis except the very mild should be operated upon at the earliest possible moment, first because of the possibility of an error in diagnosis, and secondly because I believe that there will be less destruction of tissue, and that the operation should be carried out under local anesthesia with a minimum of ether to keep the patient on the table during manipulation.

(2) "If all diagnostic measures point to pancreatic necrosis, delay is permissible until abscesses localize, cysts and gangrenous parts need removal." Yet their statistics show that operations delayed over 24 hours and up to 3 weeks have a mortality of 50 per cent. It is, I believe, important that all cases except the very mild ones be operated upon within 24 hours if it is possible to get the cases.

(3) "If diagnosis is uncertain, early operation must be done for fear of overlooking intestinal perfora-

tions." Operation within 24 hours would cover these cases.

(4) "If the attack is mild, wait for recovery and then diagnose and operate for biliary tract infection." Their statistics show that the mortality in cases operated upon more than 3 weeks after onset was only 20 per cent. It is quite evident that these cases were mild or operation would have been performed earlier. It would seem that the mortality of cases operated upon from 2 to 3 weeks after onset, 66 per cent, and the mortality of those operated upon after 3 weeks, 20 per cent, were unnecessarily high. It would seem reasonable to expect a lower mortality if all operations had been done within 24 hours.

May I diverge for a moment to mention *diagnosis* and to say that laboratory examinations, at least those in use up to the present time, should not make one give up physical examination, for every available method should be used in the diagnosis of these difficult cases. The most satisfactory aid to making such a diagnosis is the careful determination of the location of tenderness. It is not enough to say that there is tenderness in the upper abdomen. Given symptoms suggesting gall bladder disease, the diagnosis of pancreatitis should be made correctly in a high percentage of cases if there is tenderness extending to the left from the gall bladder. This can be accomplished only by meticulous care as to the amount and extent of the tenderness. Experience is necessary, of course, to make this distinction and yet a former resident, of very moderate hospital experience, made a correct diagnosis in the next two cases that were admitted after he had been taught this method of diagnosis.

I appreciate that there has been much written recently about attacks of pancreatitis causing pain, indigestion, and discomfort in the upper abdomen after cholecystectomies and cholecystostomies, but I have not seen enough of these cases to make me feel that pancreatitis following cholecystectomy and choledochostomy is of much importance. It is true that at operation I have left stones which have had to be removed at a second operation, but this has always given relief. I have operated twice for attacks of pain following operations for gall stones without finding any cause for the pain, even pancreatitis, but in spite of this there was no further occurrence of the pain after several years.

It is quite evident from various case reports that there is frequently more than one attack suggestive of pancreatitis before operation seems necessary. In 1921 I called attention to the fact that 22 of the forty-three cases of acute pancreatitis from the Massachusetts General Hospital occurred in patients without gall stones, and of these 17 had had one or more attacks of pain before having an acute attack of pancreatic necrosis requiring operation.

Archibald believes the mild attacks to be acute pancreatitis due to retrojection of nearly normal bile into the pancreatic duct, which causes an inflammation and therefore swelling, but not a necrosis. Whipple and Goodpasture (Surgery, Gynecology and Obstetrics, 1913, XVII, 591) report that in animals there may be attacks of pancreatic necrosis with absorption of the necrotic material which leave a scar so small that it is difficult to find it. How such a condition can produce the findings of deTakats and MacKenzie is difficult to understand.

"Indigestion" and slight discomfort in the epigastrium do not have much significance for me. When we consider the various operations which have been carried out for the relief of these symptoms, we wonder if these symptoms really mean much. The outstanding reasons given for such symptoms before operation have been chronic appendicitis, chronic salpingitis, retroversion of the uterus, so-called chronic cholecystitis without stones together with an X-ray showing a gall bladder which does not empty quite as the roentgenologist thinks it should, stasis in the duodenum, duodenal diverticulum, and now chronic pancreatitis either before or after operation. One is not much impressed with the value of these symptoms when they are supposed to be "cured" but such different operations. In many clinics chronic cholecystitis without stones makes up at least 50 per cent of all the gall bladder operations. One wonders why we do not all have our gall bladders out for slight indigestion and perhaps a fulness in the upper abdomen. It has been said by some surgeons that cases of chronic choecystitis without gall stones should be operated upon not only for relief of "indigestion," but also for fear they may cause pancreatitis! In spite of this great danger, Wilkie has said that he has had great difficulty in finding a bacteriologist who could find bacteria in the gall bladder walls for him, and yet he considers operation of great importance. If these symptoms are of value, why has it been necessary to do so many different operations for the relief of them, and why are patients not more often relieved by the operations?

Operations for the relief of acute interstitial pancreatitis do not seem to be necessary as the symptoms do not seem to be sufficient to make a diagnosis possible, or at least to make an operation necessary, as such a condition is rarely if ever seen at operation unless we consider Zoepffel's acute oedema of the pancreas as an acute interstitial pancreatitis.

The treatment of chronic interstitial pancreatitis is incidental to finding it in the course of operations for other conditions such as cholelithiasis, duodenal or gastric ulcer, acute cholecystitis, or some abdominal infection, and should consist, I believe, of the removal of whatever is the cause of the pain. To make doubly sure, it is important to drain the biliary system especially if there is jaundice. Many cases of chronic pancreatitis have been relieved entirely by cholecystectomy alone, without drainage of the biliary system. Long continued drainage of the biliary system has been emphasized by many surgeons, especially Deaver, but drainage for two weeks is sufficient in all the cases I have seen. Deaver recommended and carried out on several patients cholecyst-gastrostomy in cases in which jaundice had recurred or had not cleared. It has been my good fortune in about 2500 cases of cholelithiasis and cholecystitis never to have been obliged to do a cholecyst-gastrostomy for chronic interstitial pancreatitis. It seems probable that when any such operation is necessary, the condition present may be carcinoma of the head of the pancreas.

As to *preventive measures* in pancreatic disease, there is no doubt but that removal of gall stones when found is an excellent measure, but I cannot agree with those who feel that it is important to remove the gall bladder in cases of so-called chronic cholecystitis without stones, to prevent acute or chronic pancreatitis. The arithmetic of these men seems to me to be at

fault, for in my own practice I have operated upon forty cases of acute pancreatic necrosis and abscesses of the pancreas, while during the same period I have seen more than 2500 cases of cholelithiasis. That is, about 1.6 per cent of all the cases of cholelithiasis and acute cholecystitis are associated with acute pancreatic necrosis.

As the mortality of acute pancreatic necrosis is about 50 per cent, the mortality rate for these acute pancreatic necrosis cases associated with cholelithiasis and acute cholecystitis could not be more than 0.8 per cent. The operative mortality for cholecystectomy in cases of chronic cholecystitis could not be less than 2 per cent, which leaves a balance of 1.2 per cent in favor of not operating upon these cases.

While it must be admitted that there is little that is new in regard to the *treatment* of pancreatitis, we have a most brilliant piece of clinical work on carcinoma of the pancreas, for which we owe a debt of gratitude to Drs. *Whipple, Parsons, and Mullins, regardless of* whether the late results will or will not be commensurate with the brilliancy of the clinical deductions that have been made.

It must have been appreciated by every surgeon that pancreatic secretion could not get into the duodenum in cases of carcinoma of the head of the pancreas with marked jaundice, yet no one has ever before drawn the conclusion that the pancreatic duct might be tied off without doing any damage to the individual. This clinical observation has brought many cases of carcinoma of the pancreas into the field of operative surgery. Not only is the observation and proof that the patient can exist without the external secretion of the pancreas of importance, but the carefully worked out operative procedure is of great importance. (Whipple, Annals of Surgery, October, 1935).

It has taken many years to convince surgeons that the pancreas can be operated upon the same as any other organ, provided one is careful to prevent leakage and infection. In fact, it has been found that the pancreas can be incised or large sections removed without danger to the patient. To have this proof that patients can live with the pancreatic duct tied off gives the surgeon control over the whole pancreas. A large part of the tail can be removed from the tail toward the head without doing harm, and now that Whipple, Parsons, and Mullins have proved that the pancreas can be partly removed from the head toward the tail, the whole organ is under control.

Not only is this work of importance in carcinoma, but it will make the removal of cysts much more certain than formerly. Removal of a portion of the pancreas with the cyst may be done with the hope of no further trouble, for few have attempted to remove cysts of the pancreas with any feeling of certainty that they would not recur. With our present knowledge of the pancreas, removal of sufficient gland tissue to make sure that a cystadenoma or a simple cyst will not recur is of importance. Degeneration cysts or pseudocysts should not recur, and simple drainage is all that is necessary.

Probably the most spectular operations on the pancreas are those for hypoglycaemia due to adenomata or to hyperplasia of the pancreas. In addition to the adenomata, which give such striking results when removed, there is apparently a hyperplasia similar to hyperplasia of the thyroid gland. Some cases have been operated upon in which no adenoma can be found. In order to treat these cases, an unexpectedly large proportion of the gland must be removed, as in thyroidectomy, in order to reduce the insulin sufficiently to return the patient to normal. Unfortunately the problem is more difficult than in thyroid disease because of the greater risk in opening the abdomen two or more times to reduce the gland sufficiently.

In all operations for removal of a large or small part of the pancreas the great danger is in injury to the blood vessels in the region of the pancreas. Removal of the spleen may be necessary because of injury to the blood supply or to facilitate the removal of a growth.

The operation for hypoglycaemia and Whipple's operation for carcinoma of the pancreas have been the outstanding clinical advances in surgery of the pancreas in many years. Let us hope that within the next ten years the etiology, classification, diagnosis and treatment of pancreatitis can be put on a more definite basis than it is at the present time.

Thoracic Stomach with Short Esophagus and Diaphragmatic Hernia*

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"DIAPHRAGMATIC hernia" was the all inclusive term applied to a protrusion of the stomach through the diaphragm, until Bailey (1) introduced the name "thoracic stomach" to that type due to a shortening of the esophagus. There is a tendency to ascribe all of these lesions to a congenital, actual or potential defect in the diaphragm in contradistinction to the traumatic form of hernia through the diaphragm. A potential widening of the hiatus esophageus may, however, be a predisposing factor in the causation of the latter. In three patients of our series, an hiatus large enough to admit three fingers was found at the time that an operation was being performed for some other condition. Where formerly

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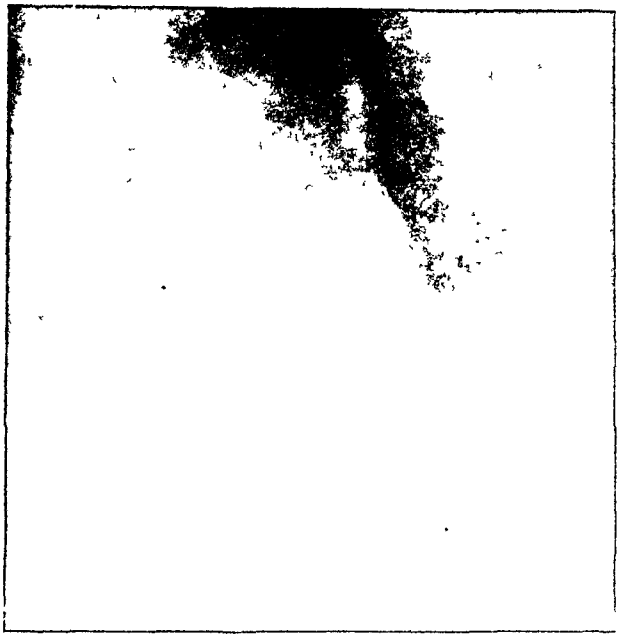


Fig. 1

diaphragamatic hernia was considered to be the more frequent lesion, it seems that the diagnosis of hiatus hernia and congenitally short esophagus is gaining in ascendency. An adherence to Akerlund's (2) classification of three types would help to clarify the situation immeasurably. There will be however, because of a lack of diagnostic methods, a large number of cases which will be unclassifiable.

Our interest in this subject was aroused by the fact that we were encountering these lesions in greater numbers, undoubtedly due to an increasing number of reports in the literature, and an increasing ability to recognize them. Therefore, when we decided to study this condition more thoroughly, we recalled as many of our patients as we could, in whom the diagnosis of "diaphragmatic hernia" had been made previously, with the purpose of trying to differentiate them into recognizable types. As we were only partially successful in our attempt, one of us enlisted the aid of esophagoscopy and later biopsic examination as suggested by Clerf and Manges (3). It is quite obvious that this kind of examination is superior to that of localizing the length of the esophagus by the level of the thoracic vertebra, although the latter is a much simpler procedure. Unfortunately we were unable to obtain the consent of all the previously examined patients to return for another fluoroscopy and still less for esophagoscopy. While we were thus enabled to increase our ability to differentiate the types, we did not acquire a corresponding increase in our facility to make a clinical diagnosis of the condition beforehand. On several occasions we suspected the lesion, only to find ourselves wrong in the majority of cases. We are inclined to agree with Ritvo (4) that in the majority of the cases it is an accidental finding without characteristic symptoms. The symptoms related by the patients are more frequently due to some other underlying cause. If more individuals were examined roentgenologically, the lesion would undoubtedly be found more frequently.

Incidence: Eleven patients were males and twenty-seven females. All of our cases were in adults. The ages ranged from 31 to 70. Only seven of these were in the seventh decade of life.

Symptoms: A restatement of the symptoms will be nothing new. We shall therefore make an analysis of the symptoms encountered in the hope of finding out which ones, singly or in combination, might suggest a diagnosis before other methods of investigation are utilized.

Twelve complained of epigastric pain, for periods varying from one to twenty-four years. In three of these the pain was worse at night, or on lying down, and in four it radiated to the left. One patient stated that the pain was distinctly worse on attempting to lift a heavy weight, Fig. 1. This patient, a woman of 51, was seen in 1933 because of pain in the right upper quadrant of the abdomen of eight years duration. She had some pyrosis which was relieved by soda bicarbonate, but no dysphagia. The gall bladder concentrated the dye normally. We mention this negative point because on X-ray examination a narrowing of the esophagus was found in addition to a large supradiaphragmatic gastric pouch. She came to the hospital for esophagoscopy and then changed her mind. This is probably a case of thoracic stomach on the basis of a congenitally short esophagus.

In the four patients whose pain radiated to the back, the lesion was of medium size in two, large in the second, and small in the third. In the last patient the esophagosopic length was 40 cm. and biopsic examination revealed esophageal tissue at that distance. The impression obtained, therefore, is that this might well be a case of para esophageal diaphragmatic hernia, which incidentally is the impression obtained on fluoroscopic examination. Another patient, female, age 51, with a medium sized gastric pouch had complained of severe pain in the left upper quadrant radiating to the back for many years—in fact as long as she could remember. The pain came on immediately after meals and was made worse by a heavy meal. Occasionally



Fig. 2

the pain occurred at night. The gall bladder concentrated the dye normally. The esophagoscopic length was 40 cm.

The mucosa at the cardiac orifice was reddened. Biopsic examination revealed gastric tissue. This is probably another case of para esophageal hernia. Three of these twelve patients had cholelithiasis.

"Heartburn" occurred in twenty-two patients, in seven of whom it was relieved by soda bicarbonate. In eight, it was definitely worse at night or occurred only on lying down, to be relieved when the patient assumed an upright position. In three of these the lesions were of medium size and associated with esophageal constriction above the gastric pouch in two. In one of these, a patient, age 56, who was afraid to lie down because of heartburn, esophagoscopy revealed an hyperemic mucosa which bled easily, and a thickening of the posterior folds at a level of 32 centimeters. In spite of this definite picture of esophagitis, her only complaint was nocturnal pyrosis without dysphagia. Another patient, a male, age 11, complained of heartburn for about eighteen years, when lying down. X-ray examination revealed a large gastric pouch with an esophageal constriction. The esophageal length was 37 centimeters. The diagnosis is probably thoracic stomach with short esophagus.

Six of these twenty patients had cholelithiasis. How much the pyrosis was due to this and how much to the gastric lesion, is difficult to tell. In the majority of cases there was no relationship between the size of the lesion and the amount of heartburn.

Vomiting, alone or with regurgitation, occurred in ten patients, and regurgitation in four. Relief of the distress by vomiting was not common. In five of these patients the lesion was small, in two large and one medium.

Pain in the chest, either of a substernal type or radiating to right or left, occurred in only 6 patients. One of these patients came to see us in 1931 complaining of irregular gastro-intestinal discomfort. Two years before, a diagnosis of chronic cholecystitis was made in Detroit by very capable physicians. At times the patient complained of severe right hypochondriac pain. About one year later he had severe pain in the left precordial region, radiating to the left shoulder and arm. The gall bladder concentrated the dye well and an electrocardiogram showed no deviations from normal. A tentative diagnosis of diaphragmatic hernia was recorded on the history, but it could not be confirmed by X-ray examination. Four years later the diagnosis of thoracic stomach and short esophagus was made at the Mt. Sinai Hospital, New York, while the patient was under the care of Dr. Winkelstein. Hurst (5) reported the case of a patient with recurrent hernia of the stomach through the hiatus esophageus of the diaphragm with pain resembling angina pectoris. Three patients in this group had dysphagia, but esophagoscopy was unsuccessful in two and not tried in one. One other patient in this group will be discussed later. In two it was undecided whether the pain was referred into the chest from calculous cholecystitis, or from the gastric pouch.

A history of dyspnea was obtained in six patients. In all of these the lesion was either of medium or large size. Goodall and Hoyt (6) lay great stress on dyspnea of a peculiar type which occurred in four of their five patients. They found a characteristic dyspnea, one occurring on the slightest effort or after eating—a sort



Fig. 3

of panting breathing—disappearing when the patient sits down and prone to be absent even on exertion, when the stomach is empty.

They divide their cases in two types—one in which the major part of the stomach is above the diaphragm, and the other in which the major part is below the diaphragm. The intense type of this remarkable form of dyspnea occurs in the first type and lead the authors to make a clinical diagnosis of thoracic stomach in two other patients, after having found a thoracic stomach on X-ray examination in the first patient who had this sort of breathing. We did not encounter this severe symptom in any of our patients because the lesions were all of the second type, with the exception of one who refused to come back for a re-examination. Six patients complained of some form of dyspnea. One in this series, Fig. 2, a woman of 38, complained of epigastric pain, nausea, vomiting, tightness and a smothering sensation of the chest with frequent attacks of dyspnea. She had stomach trouble dating back to childhood. In 1926 she was told that she had asthma. An X-ray examination revealed the largest thoracic stomach in our series. Unfortunately we lost track of her and could not get her back for re-examination or esophagoscopy. In the light of Goodall and Hoyt's report and the fact that her symptoms dated back to childhood, we are inclined to consider this case as one of congenitally short esophagus and thoracic stomach.

Dysphagia occurred in six patients. In the report of Clerf and Manges (2) dysphagia was a prominent symptom. Their patients differed from ours in that the majority came to them primarily for difficulty in swallowing. The lesions were of medium size in two, small in three, and undetermined in one. Two had indefinite chest pain and three heartburn at epigastric

pain. Esophagoscopy was carried out unsuccessfully in three patients.

They refused to return for re-examination. X-ray examination revealed a supragastric constriction. One of the patients ,Fig. 3, male, age 62, had difficulty in swallowing over a period of two years and had had repeated attacks of biliary colic. X-ray examination revealed a thoracic stomach with an esophageal narrowing and cholelithiasis. A cholecystectomy was done, at which time it was found that the hiatus esophageus admitted three fingers quite readily. The dysphagia returned later. Esophageal dilatation gave him some relief. Esophagoscopy was attempted, but because he violated instructions not to partake of fluid and denied having done so, it was unsuccessful as gastric fluid regurgitated into the esophagus at the time of examination. He refused to return for re-examination.

In attempting to *evaluate these symptoms*, we were confronted by the fact that many of the patients who had other pathological conditions, as calculous cholecystitis (11 cases), hypertension with or without cardiac involvement (8 cases), hyperthyroidism (2 cases) and syphilis (2 cases), had the same complaints as those patients with thoracic stomach without these lesions. It is, therefore, very difficult to determine upon a symptom complex which is typical of thoracic stomach. The following symptoms are suggestive: increased pain or heartburn on lying down, pain in the chest radiating to the left or down the left arm and dyspnea, neither one of cardiac origin, and difficulty in swallowing of long duration in a patient in whom traumatic stricture, carcinoma of the esophagus or cardiospasm can be ruled out.

X-ray examination: In every case the actual diagnosis was made by X-ray examination. Attempts to visualize both the hernial protrusion and the esophagus as suggested by Einhorn (7) were unsuccessful in most cases. It was necessary to give the patient some more barium and visualize both structures at the moment of the passing of the barium. This should be an excellent method for differentiation. Unfortunately a second meal of a thick paste was not always successful. We classified our lesions as small, about 3 centimeters or less in diameter, medium 4 to 6 centimeters, and large 7 centimeters or more. Fifteen were small, eleven medium and eight large.

X-ray examination alone sufficed to make a diagnosis of para esophageal hernia in seven patients, in one of whom it was confirmed by a double meal, and in six by finding the esophagus to be of normal length. In one patient dilatation of the esophagus by X-ray was found and esophagoscopy revealed shortening. In six patients the finding by X-ray of a constriction of the lower end of the esophagus with a supradiaphragmatic gastric pouch suggested the presence of a short esophagus. Only one of these was confirmed by esophagoscopy alone, as the other patients refused to return for further examination.

Esophagoscopy was employed for the purpose of getting information about the condition of the esophagus, determining its length and later to obtain specimens of tissue at the level at which gastric mucosa was seen. It is ordinarily accepted that the distance from the teeth to esophagus is 40 centimeters. However, this may vary some with the heighth of the patient. In this report 39 to 40 centimeters are accepted as normal, except in those patients in whom a constriction is found at the lower end of the esophagus, in addition to roentgenological evidence of a supradiaphragmatic pouch of the stomach. Because of our inability to have all patients with this possibility return for esophagoscopy, we are unable to furnish any definite statistics on this point. Esophagoscopy was carried out in fifteen patients. In nine it was responsible for the diagnosis, and in six it confirmed the diagnosis made by X-ray.

The results of *biopsic study* in nine patients showed that gastric mucosa was obtained in three patients at a level where the esophagus should be, and esophageal mucosa in the others. Because of a constriction at the lower end of the esophagus in three cases, it was impossible to enter the stomach. X-ray examination, however, revealed the fact that the esophagus was constricted above a small protrusion of the stomach above the diaphragm. In some patients in whom the esophagoscope was passed to the 39 or 40 centimeter mark, there is still the possibility of the lesion being a paraesophageal hernia—that is, a real diaphragmatic hernia. Many more studies will be necessary to determine this fact. In all cases where a biopsy was made, the esophagoscopic diagnosis was confirmed. It seems unlikely that this method of examination is necessary except in extremely doubtful cases.

SUMMARY AND CONCLUSIONS

1. Thirty-nine patients were seen with the diagnosis of some type of thoracic stomach. In 7 the lesion was a paraesophageal hernia. This diagnosis was confirmed by X-ray examination and finding the esophagus to be of normal length. In one it was confirmed at fluoroscopy by a double meal. Many may question the frequency of this lesion, and rightly so, because of the tendency to consider most of them to be due to congenital shortening of the esophagus.

2. In nineteen the diagnosis was thoracic stomach due to a shortened esophagus. In six a constriction of the esophagus above the gastric pouch was seen. In 9 the diagnosis of short esophagus was made or confirmed by esophagoscopy. In one the history of difficulty in swallowing and finding a constricted esophagus by fluoroscopy, and in another the history of gastric disturbance from childhood on, without an esophageal constriction, were sufficient to make the diagnosis. In one patient the diagnosis was made elsewhere. In 12 it was impossible to determine the kind of lesion found.

3. A clinical diagnosis of thoracic stomach should be suspected in patients presenting the above mentioned symptoms over a long period of time, in whom other pathological conditions can be ruled out.

4. The thoracic stomach of unknown type requires more careful examination by various methods, as X-ray, double meal and esophagoscopy for differentiation.

5. Biopsy is only a confirmatory procedure and is unnecessary where esophagoscopy is satisfactory.

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DISCUSSION

DR. JOHN H. FITZGIBBON (Portland, Oregon): Dr. Bloch did not mention bleeding as a complication of diaphragmatic hernia. I have seen over thirty cases, out of which group two patients have had severe hemorrhages and a history suggestive of peptic ulcer, but with no X-ray evidence of abnormality other than hiatal hernia. It is reasonable to assume that they were bleeding from ulceration in the herniated part of the stomach. Both responded well to ulcer management and are continuing treatment. The recurrence of ulceration without hemorrhage in these patients is something that should be given serious consideration. If stools are routinely examined, we shall find occult blood continuing over long periods in many. Secondary anemia is occasionally an outstanding feature.

Dr. Bloch's paper brings out the fact that hiatal hernia is rather common, and I feel that we should emphasize the importance of horizontal fluoroscopy. No gastro-intestinal X-ray examination is complete unless the patient is examined lying flat or with the head lowered. Upon taking a deep breath and straining, barium will be seen to "pop" up through the hiatus into the hernia. If this sort of examination is made routinely, particularly in people who have been suspected of having gall bladder disease or who have been operated upon for supposed gall bladder symptoms without subsequent relief, hiatal hernia will be found much more commonly than is generally realized.

DR. RALPH C. BROWN (Chicago, Illinois): Adding to what Dr. Fitzgibbon has said, I am convinced that peptic ulcer occurs in association with these hiatus herniae, possibly resulting from the ischaemia produced in the mucosa of the stomach at the point of constriction. I have seen massive hemorrhage in association with at least one such case, and in two other cases there was such a degree of perigastritis at the point of constriction of the stomach as to involve the esophagus in scar-tissue to such a degree as to produce obstruction which required dilatation.

I think the probable association of peptic ulcer with hiatus hernia is something which at least should be kept definitely in mind. It is difficult to see the ulcer lesion when it exists at the point of constriction, so I am not able to state with absolute certainty that peptic ulcer occurred in the three cases to which I have referred. However, all three of these cases responded immediately and permanently to the therapeutic test of routine ulcer management.

DR. JOHN L. KANTOR (New York City): In addition to frank hemorrhage, there may be oozing in cases of diaphragmatic hernia. This is one of the causes of obscure anemia that should be kept in mind.

There was one case of this kind in New York that masqueraded as carcinoma. It was discovered by the late Dr. Rothschild, an internist. It is well worth knowing that by examining these people in the ordinary erect position and giving them a Sedlitz powder, one may bring out a second shadow parallelling the diaphragm but higher up in the chest. This shadow represents the gas filled intra-thoracic portion of the stomach. The procedure was devised by Dr. Ball and published in the *J. A. M. A.*, October 19, 1935.

DR. LEON BLOCH (closing the discussion): None of these patients had an apparent hemorrhage, but one had a definite ulcer which we could see with the esophagoscope very distinctly and bleeding had occurred. In all of the patients in whom esophagitis was found by the esophagoscope there was no question about the diagnosis: the mucosa was red, hyperemic, spongy and bled very readily so that undoubtedly had we examined the stool we might have found blood.

In two of the patients we found not only esophagitis but gastritis extending below the esophageal gastric margin.

The method of examination, of course, is important. All of the patients were examined, either lying down or in the Trendelenburg position. In most cases it is a simple matter to examine the patient in either the right or left oblique, or in the supine position. There was no difficulty in finding the lesion. Once in awhile we were aided in finding the lesion by having the patient take a deep breath, because when the diaphragm descended the gastric pouch came up very distinctly.

Specific Food Sensitiveness*

By

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IN the time available I can report only briefly on some of the impressions that stand out strongly from the experience of the last few years. First, I would like to say that there is no question in my mind about the need for the development of a greater interest in specific food sensitiveness on the part of gastro-enterologists and, for that matter, of physicians practising in every field of medicine. We should all of us be grateful to the allergists for having opened our eyes to the possibility of relieving several distressing syndromes, such as migraine and mucous colitis, by the forbidding of certain foods.

Dietitians also could profit from conversion to the view that the *digestibility* of a food may at times be much more important to a patient than is its content of vitamins or calcium or iron. So far, most of the books on dietetics either ignore the subject of digestibility or else dismiss it with a few words, and the individual dietitian, unless she has been specially trained under an allergist, is likely to have little patience with anyone who claims that he cannot take milk or eggs or spinach or orange juice. Time and again highly allergic patients have told me of the miserable experiences they have had in hospitals where, after an operation, they were forced to continue eating the so-called "health foods" long after the prophesied vomiting or painful bloating appeared.

Perhaps I should say that the outset that I have no intention of joining the group of enthusiasts who seem to believe that nearly every disease is due to food allergy. Perhaps when I have learned more about this subject my percentage of miracles and cures will be higher, but as yet I must admit that I meet with far

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more failures and disappointments than with successes. In many cases I haven't even the desire to start experimenting with diet because the history suggests so strongly that the troubles are not due to the nature of the food eaten. This is particularly true when short spells of discomfort alternate with intervals of weeks or months when the patient is able to digest anything. In such circumstances, if the inciting factor were a food it would have to be one seldom eaten, and in such circumstances the patient would probably have recognized his idiosyncrasy. Or a woman with migraine will tell me that her headache comes only with menstruation or when she overworks or sits up late waiting to scold a wayward son, or when she takes a long automobile ride.

To be sure, in some of these cases migraine or vasomotor rhinitis may come as the result of the combined action of two insults, and the removal of wheat or some other food from the diet may enable the brain or the nose to withstand the effects of fatigue or menstruation or dust. Especially when, in a given case, facts in the history have warned the physician that the symptoms are probably not due to food, he will feel disinclined to keep on experimenting with narrow elimination diets unless they soon show definite signs of bringing relief.

Although, as I have said, I meet with more disappointments than miracles, when the miracles come they are so delightful that I feel that we physicians all owe it to our patients, to our reputations and to the good name of scientific medicine to keep constantly on the watch for cases in which remarkable successes can be attained.

Perhaps it would help if I were to stop for a moment to recount briefly three or four of the experiences which have convinced me that even those of us who are much interested in food sensitiveness must still be failing to recognize cases of the disease and must be turning away patients whom we could easily cure.

Thus, a few months ago, I saw with Doctor Rozendaal a young man who said that he was well until about seven years before, when he was a sophomore in college. He then began to have so much flatulence, abdominal pain, and mental cloudiness that study became almost impossible and he had to go home. There, in spite of treatment by many physicians, he continued to suffer so much that he could seldom do any work. My impression from looking at the man and listening to his story was that his mental deterioration was his part of a poor nervous inheritance which had produced a syndrome suggesting mild epilepsy in a brother, and I had no hope of helping him. All laboratory and roentgenologic reports were negative. It was only a forlorn hope that led us to experiment to see if an elimination diet would affect the abdominal distress. To our astonishment, he returned in forty-eight hours a different person. For years dull, apathetic and discouraged, he now was bright and wide awake, his ambition had returned, his head had become clear, his abdominal discomfort had disappeared, and he had begun to eat and to gain in weight. Soon he was able to work all day on his father's farm, and after a few months he wrote to say that his health was good so long as he avoided certain foods.

A physician was seen for several years with severe hunger pain, so typical of ulcer that it never occurred to me or to any of my colleagues to suggest a study of food sensitiveness. At times the pain was so severe that milk had to be taken every hour. Eventually the abdomen was explored, an ulcer could not be found, and pyloroplasty failed to give relief. In February, 1935, after an attack of asthma, skin tests were made and a tremendous sensitiveness to milk was discovered. Removal of this food from the diet brought immediate relief, and later it was found that orange juice and chocolate also had to be avoided. Since these three offending foods have been excluded from the diet, the patient has been perfectly well. I have seen now several such cases in which a desperate effort was being made to cure hunger pain with the very thing which was causing it; namely, milk!

For several years a man kept coming to The Mayo Clinic complaining of a sort of narcolepsy severe enough to cause him to fall asleep at the wheel of his car or while talking business in his office. All attempts at treatment had failed. Last year, when careful questioning revealed the fact that most of his trouble followed breakfast, I suggested that he go without this meal and then, if that helped, he could test one food at a time until an offender was found. I had little hope that he would find a cure this way and I had forgotten all about the man when, some months later, his home physician wrote that the avoidance of cream had worked a complete cure.

This brings me to another point that still deserves much emphasis, which is that *hurtful foods so often injure or irritate the brain.* To my surprise, once, while trying to cure hives in a man who had not worked for years on account of distressing feelings in his head, I accidentally cured the "insanity" and the man went back to take charge of his business again. On another occasion I saw a man in *status epilepticus* which was due apparently to his having gorged himself on strawberries, and I have seen people who knew that they would develop a vile temper if they ate certain foods. We all know that nightmares can follow the eating of a "Welsh rabbit," we know that splitting headache or migraine can follow the eating of chocolate or cheese, and I happen to know from personal experience that the eating of chicken or eggs can give rise to weird visions, annoying dopiness and even signs of meningeal irritation.

Besides the few cases in which a cure comes as a welcome surprise, there are, of course, the many in which it is to be expected because the patient has already learned that one or more foods will produce the symptoms complained of; he continues to suffer only because neither he nor his physician knows how to go about the business of discovering all of the noxious agents. If he is intelligent, all he needs to start him on the road to recovery is a little instruction in home detective work.

Obviously we cannot afford to waste time hunting for food sensitiveness in every patient, so the next question is: in what type of case should we be particularly careful to look for it? My impression now is that *we should look carefully for food sensitiveness* whenever the symptoms of abdominal distress point to the presence of an overly-sensitive colon, or when they are vague or unusual, or whenever careful examination fails to reveal any sign of disease in duodenum, stomach, gall bladder or appendix. We must study the diet in every case of true flatulence or bloating, and

we must look for food sensitiveness in some cases of migraine.

I doubt if it pays to study diet in every case of migraine because so often the history tells us that we are not likely to get anywhere along these lines. The headache may come only when the woman is menstruating or when she is very tired or has had an emotional debauch or we may see at a glance that we are dealing with a psychopathic or markedly asthenic person or one whose brain has been made so irritable by overwork, worry, grief or pain that the little "explosion" that causes the attack can take place every few days without the help of any extra insult, such as can be derived from food. This type of case is so common that I doubt if any large percentage of people with migraine can be relieved by dietary [illegible].

Occasionally I can help a patient with [illegible] but there are [illegible] whom I do not help [illegible]

[illegible]

[illegible] hours. This is to be expected from the fact that when a patient eats some harmful food the symptoms generally appear within a few hours. Accordingly, when a patient returns after having been for forty-eight hours on a narrow elimination diet and says that he is no better, the physician must not ask him to keep on for a month but must face the situation immediately. He must either accept defeat and tell the patient to return to his usual habits of eating, or else he must continue experimenting with substitutes in the elimination diet. If this does not help the patient can fast for a few days.

Ordinarily I start patients on a diet of lamb, rice, butter, sugar, and canned pears. If after a few days their distress persists, I may leave them for two days on nothing but maple sugar, or I may ask them to fast. If after this they still have their distress, I lose faith in my ability to help them with diet. Rowe tells me that sometimes in cases of wheat sensitiveness it takes ten days or a month to get the offending protein out of the system, but if it took me that long to help a patient with diet, I would suspect that the relief that came was due to some other factor such as rest, unconscious psychotherapy, or a spontaneous remission of symptoms.

Even when the elimination diet fails to help, it often gives much valuable and even decisive information as to the nature of the patient's troubles. Particularly in the case of women, one can learn so much from the way in which an individual faces or fails to face the little annoyances associated with the dieting. Often she frets so much, she acts so unreasonably, and she shows herself so irritable and so lacking in backbone and good sense that the diagnosis of "Fox's disease" can promptly be made. For those who are not acquainted with Fox's disease I will say that, one morning, [illegible] asked [illegible] Fox, what he thought [illegible] the matter with a certain woman whose case he had just been working up. The answer was, "Well, doctor, it looks to me as if she were just a plain damn fool!" The chief was so entirely satisfied with this diagnosis that thereafter, in that hospital, the particular syndrome was known as Fox's disease.

Another point that has been impressed on me time and again in the last few years is that commonly the skin tests not only fail to help the physician in his search for offending foods, but sometimes the [illegible] of a few positive results is actually a misfortune because both the patient and his physician put such a [illegible] faith in them. In many cases it is almost impossible to get the patient to touch the [illegible] foods again. I have spent hours trying to get these people [illegible] that the reaction of the skin [illegible] a trustworthy test. In [illegible] experiment of eating the suspected food to see if this makes the symptoms [illegible] the food to see if this brings relief. [illegible] canned pears? Because the skin reacted to it. Sometimes when the tests are repeated the skin is found to react to a different set of foods.

The difficulty is that we human beings are all a bit lazy [illegible] thinking and reasoning, and hence wherever possible we cling to a laboratory diagnosis which we hope will save us from having to work one out for ourselves.

SUMMARY AND CONCLUSIONS

To sum up, then, although there are more disappointments than miracles in the search for and the cure of severe manifestations of food sensitiveness, the miracles are so gratifying when they come that, each time, the clinician will resolve to spend more time looking for them. The field is still much neglected;

more diets must be fitted and fewer handed out ready made.

A good history will often show that the diet is probably not the cause for the patient's discomfort. Patients must not be left too long on narrow elimination diets; such diets are for testing and not for treatment.

Some cases of diarrhea and pseudo-ulcer are due to the milk that is taken by way of treatment, and not infrequently certain foods irritate or greatly depress the brain. Somnolence after meals can be due to a particular food, and canker sores in the mouth can be produced by food.

Efforts to use an elimination diet are often instructive in showing the physician that he is dealing with an unreasonable, overly fussy, querulous, or psychopathic person.

Food sensitiveness is not necessarily allergic or due to protein. Perhaps partly for this reason, skin tests are of little help in finding the foods that cause indigestion.

DISCUSSION

DR. ARTHUR F. COCA (Pearl River, New York): Food sensitivity is limited to the group of familial or atopic allergy in which are associated hay fever, asthma, the urticaria due to foods, atopic dermatitis, gastro-intestinal allergy, migraine and others.

In the typical case (such as hay fever) antibodies—those peculiar atopic antibodies of the human being—are regularly demonstrable in the blood and indirectly through the positive skin test. The positive skin test appears only when these antibodies are present in the blood. They are often entirely absent, for some reason that we do not understand; in such cases the skin test results negatively.

Food sensitivity can be at the bottom of any of these many clinical varieties. Some of them are associated with a positive skin reactivity and others not. If the clinical form of the food sensitivity is asthma or hay fever, or atopic dermatitis, the skin test is quite regularly positive.

I have included atopic dermatitis (neurodermite) among the clinical varieties of food sensitivity in which the skin test is frequently positive. This statement must be considerably qualified by the further remark that the direct skin reaction in this condition is almost always so weak that it cannot be used diagnostically. However, a means has been developed by Matthew Walzer in Brooklyn of magnifying this weak reaction in a way to make it a thoroughly practical and reliable specific test. This means is the indirect test, which is performed with the technic of Prausnitz and Kuestner. The test is carried out as follows:

Serum is obtained from 5 to 10 c.c. of the blood of the patient by aseptic defibrination and centrifugation. One-twentieth c.c. of the serum is injected intracutaneously in about 50 well-separated sites in the upper arm of a substitute, who must not be allergic. Three days later these injected sites can be tested with the intracutaneous method with the usual food extracts, an identical control injection being made in a normal skin site in the same skin. In comparison with the negative result of the control test, slight degrees of reaction can be recognized as diagnostic which could not be accepted as significant in the direct test in the patient's skin.

By this means, Dr. Walzer states, about 60 per cent of subjects of neurodermite can be relieved by the avoidance of the indicated foods.

Notwithstanding the valuable contribution of Dr. Walzer to the technic of skin tests in the development of his indirect test, it still remains true, as Dr. Alvarez says, that in many cases of food sensitivity, especially urticaria, allergic headache and gastro-intestinal allergy, the skin test is of very little use. It is in such skin-negative cases that the physician must fall back on the trial diet plan.

The trial diet plan can succeed only if we possess a criterion of reactions, like the wheal in the skin test, that is diagnostically significant. The criteria under the trial diet plan are, of course, the clinical symptoms of food sensitivity. Such symptoms may be immediate or delayed. Immediate symptoms are gastric pain, headache (which may occur within a hour after the ingestion of the offending food), swelling of the lips in some instances, and a peculiar sensation of the mucous membrane of the tongue, which can be very acute. Vomiting is seen in some cases. The more violent symptoms should be avoided, if possible, by administering at the first trial only a small quantity of the food to be tested, where such symptoms are feared.

I have for some time been making use of another immediate symptom which seems heretofore to have been overlooked. This is tachycardia. I do not know how often this appears. It happened to be prominent in the first four cases of food allergy that I have had occasion to study. The symptoms in all these cases were gastro-intestinal or migraine. The tachycardia can range from a rate of 80 or 90, lasting for some hours after the ingestion of the offending food. In one case that had recently suffered a coronary thrombosis, the pulse rate has risen to 160 or 180 or more within a half hour after the injection of minute quantities of the offending substance. Three of these cases could be completely relieved of their symptoms by elimination of foods through the use of the criterion of tachycardia.

Delayed symptoms are more difficult to use as criteria of reactions. These are urticaria, diarrhea, bleeding from the intestinal tract. (This latter symptom may be more frequent than is generally known because patients are not advised to examine the stool for gross evidences of bleeding). Dizziness is a delayed symptom; also extrasystole, which may be the sole symptom of food allergy in some cases. A feeling of lassitude is a distinct delayed symptom in some cases.

In the application of the trial diet principle, all plans heretofore recommended have exhibited a common error which may explain some, at least, of the many failures encountered in the use of this principle. This mistake is the illogical one of trying more than one food at a time. Different allergists recommend different combinations of food in the initial test. The successes under all these plans represent merely those lucky individuals who happened to be sensitive to relatively few foods which were not included in the first selection.

Another circumstance which has no doubt interfered with the successful application of the trial diet principle is the fact that there are allergenic foods which have not been recognized as such by even the allergists. Among these may be mentioned gelatin, which, according to the chemists, contains no native protein but which, nevertheless, can be a violent food allergen. Another allergenic food that has been largely overlooked is sugar, both from cane and from beet. There is relatively very little protein in sugar. When the protein is collected out of a solution of sugar by the process of ultrafiltration, it is found that there is something over 100 milligrams of it in 200 pounds. On the basis of the established fact that about 1 per cent of negative protein in solution will find its way through an ultrafilter when the ultrafiltration has proceeded for a period of about 48 hours, I have been able to calculate that 1/100,000 of a milligram, or possibly less, of sugar protein may cause disagreeable allergic symptoms (tachycardia, dizziness and headache) when that quantity is given daily over a period of two days.

The logical plan of applying the trial diet principle must be, first, to withhold all food until the symptoms disappear and, secondly, to administer one food at a time in ample quantity, each food being added only after the preceding

one has been given a test of not less than three or possibly two days. The period of starvation is irksome to most patients, as is also the initial period of three days when the patient is receiving only one food. With this difficulty in mind, I have hit upon the idea of providing a small basis of non-allergenic food to tide the patient over the initial period. This basis is provided by an ultrafiltered sugar solution that has been concentrated by boiling to syrup form for preservation, and ultrafiltered lemon juice, which must be preserved in sterile form after Berkefeld filtration. A patient can be kept quite satisfied for several days on nothing but this non-allergenic sugar and lemon juice, which can be taken in the form of lemonade with or without carbonated water.

DR. ANTON OELGOETZ (Columbus, Ohio): I would like to emphasize this idea of indigestion in its relation to food allergy. About six years ago we became interested in the subject of food sensitization. Perhaps you have read some of our papers. The subject finally got down to a matter of digestion.

As has been stated, Walzer has shown that whole proteins are normal constituents of normal blood. We have shown that the blood stream always contains the three pancreatic enzymes, amylase, protease and lipase in a definite concentration of two-tenths by the test which we have suggested. This concentration never varies throughout the day or night and is uninfluenced by sleep, intake of food or exercise. We have made 15 minute determinations on many, many cases, and always have found the pancreatic enzymes present in the normal concentration of two-tenths.

We, long ago, came to the conclusion that there is no specific sensitivity to foods. All proteins, all carbohydrates and all fats are enzymotically and physiologically similar, and the three pancreatic enzymes are hetero-lytic. The reason that this mistake was made, in our opinion, is because, as Dr. Alvarez has suggested, two factors are involved which have not been taken into consideration. Dr. Alvarez said that ordinarily, when at home, quite and relaxed, he does not have difficulty when he eats chicken, but when he is away from home, under unusual mental stress and strain he becomes allergic to chicken. He has suggested that indigestion might have something to do with his difficulty. We have shown on many patients that nervousness produces a temporary pancreatic hypofunction, or in some cases, a complete achylia, which is the cause of the phenomenon.

According to our conception, digestion starts in the stomach and upper bowel, where proteins are split all the way down to amino-acids. But not completely so. As Walzer has shown, much of the protein is absorbed as whole protein which is toxic to cells. It is the serum enzymes which complete digestion in the blood stream and prevent the serum proteins from reaching the cells in an unsplit state which cannot be used as food. Whole proteins are toxic, while the split products of proteins are non-toxic to cells, and it is the serum enzymes which prevent all of us from being food allergic all of the time. Food allergy results from too much food, more food than can be hydrolyzed by the available serum enzymes.

Variations in gastric secretion — hypersecretion and achylia—are commonly recognized conditions, but it is strange that we have never heard much about pancreatic hypofunction and achylia. Surely the pancreas must vary in the quantity and concentration of its secretions, just as does the stomach. We check our cases routinely for pancreatic function, by the test which we have described, and we find that pancreatic hypofunction and achylia are rather common. Since doing this test routinely, we are finding that many cases which we formerly labelled "functional" or "neurosis," or urticaria, or angio-neurotic oedema, are really food allergy, secondary to pancreatic dysfunction.

I wish to emphasize that there are two types of allergy caused by two different underlying mechanisms. One type is a true chemical irritation. The action of poison ivy on the skin, for example. The underlying mechanism of food allergy however, is different; it is a true indigestion, which results when more food is taken than can be split by the available pancreatic secretion. This mechanism is secondary to pancreatic hypofunction or achylia.

DR. IRVING GRAY (Brooklyn, New York): Dr. Alvarez has called attention to a subject that is attracting a great deal of interest. The mechanism responsible for "Specific Food Sensitiveness" is not clearly understood. We may postulate that there is either a direct action of the specific offending food in its unaltered state upon the mucous membrane of the gastro-intestinal tract or that the offending substance is absorbed into the circulation and then acts upon the mucous membrane of the intestinal tract. It is probable that both factors come into play: 1—a direct action by the food on the mucous membrane and 2—a systemic factor.

The cramps and diarrhea that occur immediately after the intake of a specific food to which the individual is sensitive, suggests the absorption of some product possibly in an unaltered state high in the digestive tract and an effect upon the small bowel and colon by way of the circulation.

Perhaps the absorption of an unaltered protein directly into the circulation may be responsible for many of the symptoms associated with, "Specific Food Sensitiveness." That protein in an unaltered state is absorbed from the gastro-intestinal tract has been proven by Dr. Matthew Walzer. During the past three years I have been associated with Dr. M. Walzer in studies on the absorption of unaltered protein in humans who have disease of the gastro-intestinal tract. Last year our paper was read by title before this Association. In that publication we called attention to the fact that the rapidity of absorption of unaltered protein is related to gastric acidity. The rate of absorption was shortened in patient's with decreased gastric acidity and prolonged in those with hyperacidity.

Three days ago we presented another paper on this subject before the Society for the Study of Asthma and Allied Conditions. We presented results on a group of patients in whom the protein meal was administered into the duodenum via the duodenal tube. Comparative studies showed the rate of absorption of unaltered protein to be somewhat faster when the test meal was administered intra-duodenally than when the food was taken by mouth. We were again impressed by the evidence which indicated that absorption following the duodenal test meal was prolonged in those with gastric hyperacidity and accelerated in patients with hypoacidity. In a future publication we will present our findings of the absorption of unaltered protein from the rectum.

The technique for studying the absorption of unaltered protein is an immunologic one and is the same as that which was used by Dr. Walzer in previous studies with egg and fish antigens. Peanut was the protein chosen for investigation in the present series because a serum particularly suitable for the study of this antigen was available at the time.

Peanut was excluded from the diet of the subject for 24 hours preceding the experiment. The subject was then passively and locally sensitized on the forearm by the intracutaneous injections of .05 c.c. of a 1-10 dilution of "C" serum. This serum had been obtained from a patient who was extremely sensitive to peanut and who manifested a marked reaction to intracutaneous tests with this antigen in very high dilution. One or two days later, the subject reported early in the morning without breakfast for the peanut test meal. The latter consisted of a "milk" made by dissolving 10 gms. of raw ground peanuts in 30 c.c. of water to which was added 1 gms. of sugar and .05 c.c. of oil of cloves. Shortly after the ingestion of this meal, a

reaction developed at the sensitized site, which usually consisted of pruritis, erythema and wheal formation. The onset of this reaction marked the entrance of the undigested peanut protein into the circulation.

The absorption time of each subject was measured from the time the test meal was taken to the first objective symptom noted at the sensitized site, namely erythema or wheal.

Sufficient proof has been accumulated to show that unaltered protein is absorbed directly into the circulation and that the rate of absorption is influenced by the degree of gastric acidity. Absorption time is shortened in individuals with decreased acidity and prolonged in individuals with hyperacidity.

Coca and Grove have pointed out that "the atopic reagin is specific. In the blood of individuals sensitive to more than one substance, more than one reagin can be demonstrated." Evidence that the protein responsible for the local reaction is in an undigested state has been shown recently by Alexander, in animal experiments.

DR. LEON BLOCH (Chicago, Illinois): I would like to ask Dr. Alvarez what experience he has had with this thrombocytopenia and allergy?

DR. WALTER ALVAREZ (closing the discussion): The ideal elimination diet, of course, would be no diet at all, or a complete fast, but most patients are a bit too fussy for this, and so we compromise. Occasionally when I want to learn quickly whether or not some symptom such as daily headache is due to the eating of food I ask the patient to eat nothing but maple sugar. When after several days of this, symptoms persist they are not likely to be due to food. In years I have met only a few people who seemed to be sensitive to cane or beet sugar. Theoretically a person sensitive to cane sugar should not be sensitive to beet sugar, but whether this is true or not I cannot say.

Dr. Aaron asked me why I use lamb, rice, butter, sugar and canned pears. I do because these foods rarely seem to bother people, and with them I can supply protein, carbohydrate, fat and dessert. Lamb seems to bother people much less frequently than beef does, and rice rarely offends.

A person would probably have to be very sensitive to milk in order to get discomfort out of a well-washed butter. Few people seem to be sensitive to pears.

Theoretically arrowroot, tapioca, and other such starches of foreign origin would be good foods for inclusion in an elimination diet because they are used only in small amounts. Unfortunately, cooks are not accustomed to preparing these substances without adding milk and egg.

I know of Vaughan's work and have been interested in it, but I haven't experimented with it. It seems to me that we can save time and expense by testing each food by its reactions on the patients' comfort and not on his white count.

I doubt very much if many of the disturbances due to food are allergic in nature or caused by protein. I feel sure that there are other substances in foods that can cause trouble. It may well be as someone suggested that some of our troubles are due to a stoppage of pancretaic digestion. Such stoppage may produce hunger pain in some persons by eliminating one of the fluids that dilutes and neutralizes the gastric acid.

I have been told by some physiologists that the pancreas is very sensitive to inhibiting influences arriving by way of the nervous system. Others deny this. I agree with Dr. Oelgoetz that we ought to make a careful study of pancreatic achylia and the causes which produce it.

Certain Newer Methods of Treating Peptic Ulcer*

By

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NO definite standardization of medical regimens for the treatment of all peptic ulcers has been accomplished, nor do I expect that this will ever happen. It is questionable whether peptic ulcer should be considered a specific single disease entity. It is a disturbance with such varied histopathologic features and the factors important in its etiology are so variable that the treatment of the condition will remain a problem specific in individual cases. Yet the search for the Golden Fleece, the panacea, goes on, and with every change of season there appears some new and ingenious therapeutic masterpiece. Patient's hopes are raised only to be crushed by subsequently recurring episodes of distress. From time to time therapeutic measures of a more promising nature are developed. It is my purpose in this paper to consider some of these and to attempt an appraisal of the principles on which their alleged usefulness depends.

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CERTAIN FACTORS OF KNOWN IMPORTANCE IN THE GENESIS OF PEPTIC ULCER

To treat peptic ulcer symptomatically is to apply tape to a leaking pipe; nothing lasting is accomplished by such a procedure. There must be a determinate plan in treatment which seeks to control or eradicate forces of recognized importance in the causation of this disease. Before proceeding to the discussion of what might constitute a reasonable yardstick with which to measure the methods of ulcer therapy considered in this paper, it would be well to scrutinize some of the experimental lessons which physiologists are able to teach with regard to the disease. Correlating these with clinical experience makes it obvious that certain principles pertaining to this problem must be recognized and contended with if any success in treating peptic ulcer is to be expected.

Gastric acidity and tissue defense. Although there are many inter-related factors which are important in the causation of ulcer, these ultimately resolve themselves around two: the one inherent in the ulcerating

potentiality of acid-pepsin, the other maintained in the defenses which the tissues possess and by which they protect themselves against the eroding action of the gastric chyme. It would seem that the alternating activity and quiescence which are so characteristic of such lesions would be evidence of two forces, the one of aggression and the other of defense, and that the outcome would depend on which factor was dominant at any particular stage of the life cycle of peptic ulcer.

Physiologists have demonstrated that the component fraction of gastric juice which can produce erosion is inherent in the acid-pepsin factor. The eroding tendency seems to fluctuate, not with variations in peptic concentration, but with the concentration of hydrochloric acid. Tissues laved in pure undiluted gastric juice are very likely to undergo erosion. Tissues which in their normal physiologic existence are regularly exposed to the acid chyme, however, possess definitely more resistance to the eroding action of acid than those which are not normally exposed to gastric chyme. Gastro-duodenal mucosa is more resistant to the processes of erosion than are other tissues. It has been suggested that the first factor of defense lies in the living gastro-duodenal cells themselves.

The neutralizing effect of alkaline blood in mucosal capillaries, the protective action of gastric mucus, and the presence of alleged antipepsin in its gastric mucosa have been considered as a possible explanation of the obvious mechanisms of defense in gastric tissues. An important factor responsible for the increased resistance of the duodenal cells to ulceration is inherent in the glands of Brunner, which under the necessity of neutralizing acid chyme suffuse the duodenal membranes with a profuse amount of an alkaline mucoid secretion. Nor must the protective importance of the secretions which are poured into the duodenum by organs which are extrinsic to the gastro-intestinal tract be underestimated. Bile and pancreatic juice have been shown to be of definite importance in protecting duodenal tissues against erosion by acid chyme. Furthermore, it is suggested that it may be one of the functions of certain hormones elaborated by the wall of the upper portion of the intestinal tract, among which is enterogastrone, to retard the gastric secretory rate. Although the duodenum has a remarkable reserve function in its capacity to neutralize and to buffer acid, it has been shown by Mann and Bollman (1), Baker (2), Florey and Harding (3) that it will break down under the necessity of neutralizing without interruption of the acid chyme. Ordinarily, in the daily physiologic fluctuation in the curves of gastric acidity there are alternate periods of rapidity and retardation in the secretory rate, thus giving the cells bathed in this chemical atmosphere "breathing spells" during which the forces of defense can be adequately reëstablished. Physiologists have shown that the continuous feeding of hydrochloric acid is likely to cause the eventual break-down of cells called on to resist the digestive action of the gastric chyme.

Corollaries for these experimental observations are obtainable in clinical experiences with certain patients harboring peptic ulcer, particularly those found to have duodenal or jejunal ulcers. The gastric secretory rates of such patients are usually accentuated, particularly during or preceding periods when there is definite activity of the ulcer. Following ingestion of such stimulating substances as histamine, patients with peptic ulcer frequently continue to secrete a highly concentrated acid for considerable periods after a drop in acidity would ordinarily have been expected. If such cellular behavior actually obtains in response to other stimuli, it would be obvious that the gastro-duodenal defense mechanisms of patients with peptic ulcer might be forced to exert themselves accordingly. It seems logical that the activity of these mechanisms of defense would have to fluctuate in proportion to changes in the potency of the mechanisms of aggression.

Unquestionably one of the important causes of cell dissolution which results in peptic ulcer lies in the exhaustion of the defensive powers of the cells: they may have used up their own as well as all available reserve sources of defense. The forces of erosion, through the utilization of an inherent chemical factor alone, can break down normally resisting tissues and cause ulceration. There is no reason to assume that human tissues behave differently.

Although local chemical and mechanical reactions in the stomach and doudenum are probably of the greatest intrinsic importance in the formation of peptic ulcer, ulceration can in all probability be influenced by other factors, of which several seem of pertinent importance:

The first of these factors is diminished resistance of tissue to acid aggression. If normal tissues can disintegrate under the prolonged bombarding influence of highly aggressive acid chyme, it is not difficult to assume increased liability to ulceration in tissues deficient in the mechanism of defense. This may be attributable to some congenital inadequacy in the tissues themselves as suggested by Smithies (4) and others, or to some acquired disease invading the tissues, such as inflammation or infection.

Next in importance are systemic-neurogenic factors. Certain individuals have an increased tendency to the formation and reformation of peptic ulcers. Efforts to catalogue and to categorize these systemic-neurogenic factors into definite groups by various physical measurements have not been successful because the distinguishing features seem more psychophysiologic than physical and anatomic. A striking uniformity of temperament is noted in certain groups of patients who have peptic ulcer. They are alert, attentive, keen. They are often introspective, suspicious, sensitive and given to periods of worry and depression. The periodicity of symptoms in cases of ulcer frequently is determined by variations in the psychophysiologic influences incident to the patient's daily experiences. During periods of unusual worry and tension, symptoms are likely to originate or to be reëstablished. Marked elevation of the gastric secretory rates is often noted during periods of excitement and tension, and it may be that one of the mechanism of the formation of ulcer is related directly to gastric chemical conditions which are thus affected by disturbances in the nervous system.

Utilization in treatment of factors important in the etiology of ulcer. A survey of the factors which seem important in the causation of ulcer permits a concentration of these into three groups: (1) factors of acid aggression and tissue defense; (2) the factor of local trauma to tissue; and (3) systemic-neurogenic factors. Although peptic ulcer may result from a single cause, it is probable that the interaction of several or all of these represent the usual formula. Now one, and now

another of these factors assuming the position of greatest importance.

Physiologic, bacteriologic, and clinical observations attest the fact that peptic ulcer is merely a local manifestation of a disturbance in gastro-duodenal tissues which in turn is brought about by various systemic causes. The patient as a whole must therefore be the subject of diagnostic scrutiny and therapeutic consideration.

The forces of erosion, although perhaps using the same weapon of offense, namely, the acid chyme, are varyingly offensive and are stimulated into action by various and varying means. In addition to making efforts to control or to assuage the acid factor, it would then be evidence that a rationale for defense against peptic ulcer should recognize such variations in offense and direct treatment accordingly.

The breakdown of tissues probably results not from one but from various causes, among which several are pertinently important. There may have been a localized anomalous tissue or vascular defect, tissue resistance and hardiness may have been damaged by local injury or by the products of infections or inflammatory disease, or tissue resistance may have been diminished by debilitating systemic disturbances or exhausted by the prolonged necessity of withstanding unusually active forces of erosion.

The tendency still remains to treat the single exacerbation of ulcer as a disease in itself when, in reality, it constitutes merely a single breakdown in the life cycle of ulcer. One successful stand against the mechanisms of aggression does not as a rule end the play of contending forces. Treatment must include some consideration of ways and means to keep dormant those forces which may be so difficult to control when they are stimulated into activity.

It is obviously quite necessary to make an individual problem of each case of peptic ulcer. A *rationale* for the treatment of such lesions must include not only a single method which is applied in all cases, but it must be sufficiently flexible so that special attention is given to such factors as are found to be predominantly important in individual cases. A general plan for ulcer therapy must include provisions for: (1) the management of complications and the control of distress, (2) the planning of a regimen to promote adequate healing of the ulcer, and (3) the prevention of recurrences.

I have spent some time in considering factors of etiologic importance in this disease in order to point out the necessity of directing therapeutic attention not to one, but to many factors which may be extremely variable. Realizing my inability to judge properly the usefulness of the new methods of treatment considered in this paper, I sent a questionnaire to a group of physicians who are particularly interested in the problem of ulcer therapy. I was interested to find that only 9 per cent were favorably impressed by methods other than those which might be considered the old approved methods of ulcer therapy.

A CONSIDERATION OF AGENTS USED IN THE TREATMENT OF PEPTIC ULCER

Vaccines. At the clinic we have employed many variations of vaccines as supplements or substitutes for other methods of ulcer therapy. Stock vaccines made from organisms known to produce ulcer in experimental studies on animals have been tried. In other instances autogenous vaccines were used. Although in a few instances we believe that the healing process was accelerated by the use of such substances we have never been convinced that vaccine therapy had an important place in the treatment of peptic ulcer. Only 2 per cent of physicians who have a large experience in the treatment of ulcer attributed beneficial effects to this type of therapy.

Nonspecific proteins. Various nonspecific proteins have been given parenterally in the treatment of peptic ulcer. These have been prepared from organisms such as staphylococci, Bacillus prodigiosus and gonococci and from crystallized plant, milk and various other proteins. It was hoped by these methods to produce local conditions about the ulcer and some mild general febrile reaction favorable to healing of the lesion. We have tried several types of foreign proteins in treating ulcer, but with no encouraging result. At times, particularly in cases in which complications are present, the administration of such foreign proteins is dangerous. It is usually not a difficult procedure to initiate the healing of peptic ulcers, and this seems to be the main reason for using such substances. Thirty-five per cent of specialists in gastro-enterology to whom questionnaires were sent had tried one or more of these foreign proteins in the treatment of ulcer. Only 8 per cent were of the opinion that they had obtained some beneficial results therefrom.

Metaphen. Metaphen is an organic mercurial compound originally elaborated by Raiziss and Severac (5), after an extensive study of the chemical compounds involving the nitro-benzine-mercury complex. Chemically it is 4-nitro-5-hydroxy-mercuri-orthocresol. Trippe (6), on the presumption that infection played an important rôle in the production of gastro-intestinal ulcer, felt that the use of strong bactericidal agent, which at the same time was noninjurious to tissues, should exercise a healing effect on ulcers. He believed that its use was also indicated because its action is not greatly diminished in the presence of proteins. Furthermore it was assumed that the toxicity of this substance was very low. A 1 to 500 aqueous solution of metaphen is used.

Although I am not at all convinced of the usefulness of this substance in cases of duodenal ulcer, I have had some encouraging results from its use in cases of duodenitis, erosive gastritis or in those of shallow gastric ulcer. It seems unquestionably true that in certain cases in which there are gastric, or perhaps even duodenal, lesions, local disturbances in tissue are of paramount etiologic importance. In such instances it is suggested that metaphen may exert a beneficial effect when administered in conjunction with other approved methods of treatment. Only 20 per cent of the physicians whose opinions I sought relative to the usefulness of this substance had tried it; 4 per cent were of the opinion that it had some value in the treatment of ulcer.

Mucin: Mucin is a substance prepared from the mucosa of hogs' stomachs. According to Fogeslon (7) mucin is useful in the treatment of peptic ulcer because it coats the ulcer and protects it against the proteolytic action of the gastric secretion; through its high combining power with free acid, mucin unites with enough hydrochloric acid not only to neutralize the corrosive action of the gastric juice, but also to

prolong the rate of dialysis of pepsin through the protective layers of mucin.

Theoretically the use of gastric mucin in the treatment of peptic ulcer seems a reasonable procedure. Mucin may well have a coating effect on the ulcer, and it is one of the natural gastric diluents. Both of these factors should contribute to the healing of peptic ulcer. It is difficult, however, to insure the maintenance of adequate amounts of mucin in the gastric content. In order to accomplish this, mucin would have to be fed at very frequent intervals, and this is not entirely practical.

I do not believe that mucin therapy regularly produces more favorable responses than do the customary methods of treatment. There are some patients, however, who in our experience at the clinic were benefited by the use of mucin when other methods of treatment failed. Various vegetable mucilages have also been added to the armamentariums of those treating peptic ulcer. Although these are less distasteful and less expensive than gastric mucin, they are less effective. Forty-four per cent of physicians to whom questionnaires were sent had tried either mucin or the vegetable mucilages. Seventeen per cent were favorably impressed with mucin and 11 per cent thought they noted some improvement following the use of the vegetable mucilages.

Synodal. Synodal is a foreign protein to which has been added lipoids and, finally, emetine. It is given parenterally. Pitkin (8), and later Cunha (9), were greatly encouraged by the results from its use. Cunha attributed the beneficial effects of this form of treatment to several reactions: "The included lipoprotein allegedly decreases gastric peristalsis, arrests pylorospasm, and produces hyperemia of the gastric mucosa, thus promoting healing." Cunha was of the opinion that emetine, by relaxing smooth muscle, reduces pyloric spasm, and he also thought that emetine might act favorably because of its "antibacterial properties." He suggested that the latter characteristic probably was the result of a change in the acid-base equalibrium of the tissues, thus inhibiting bacterial growth.

These are desirable accomplishments indeed, but we at the clinic do not believe that experience actually corroborated the hopes and expectations of those who originally were so enthusiastic about the usefulness of this substance. Of the physicians to whom I sent questionnaires only thirty-five had tried synodal; twenty of these were definitely opposed to its use and eight believed that it might have some use in treating ulcer.

"Larostidin." Larostidin is the trade name for histidine-monohydrochloride. By some method of reasoning, not entirely clear to me, Weiss and Aron (10) considered the absence of the essential amino acids in metabolism as the important factor in the causation of ulcer. Volini and McLaughlin (11) subscribed to the opinion that histidine promotes, restores and maintains the epithelial integrity of the gastric and duodenal mucosa. They felt that under certain conditions histidine, an essential amino acid, is not synthesized in the human body and thus were of the opinion that there is produced a metabolic defect which they hoped could be restored by parenteral injection of larostidin. They further suggested that histidine may stimulate the production of histaminase, which they hoped would inactivate histamine. Additionally they believed that this type of therapy reduces gastric acidity, gastric secretion and, possibly, peptic activity. A diminution in gastric motility has also been noted in certain cases.

All of these accomplishments would be desirable indeed, and it must be admitted that if such results could consistently be obtained when this treatment was utilized, larostidin would be a most valuable adjunct to ulcer therapy. I, however, have been unable to corroborate the impression that histidine consistently reduces gastric acidity; as a matter of fact I have noted the opposite effect in studies by means of the double histamine test.

My experience with larostidin, which includes cases in which the patients have been treated by me and a large number in which the course of treatment was given by others, has not been satisfactory as far as permanent results are concerned. In some instances there has been some symptomatic improvement, and distress has occasionally been promptly relieved following injections of histadine; experimental work now being carried on at the clinic with larostidin, however, is not producing the encouraging results noted by some investigators. More than 50 per cent of physicians whose opinion I sought in the evaluation of the usefulness of these substances had used larostidin in the treatment of ulcer; only 11 per cent were encouraged to continue its use.

Duodenal and jejunal feedings. It has been suggested that the most satisfactory manner of treating peptic ulcer is to pass a small tube into the duodenum or jejunum so that feeding can be accomplished beyond the area of ulceration. Thus it is assumed that the ulcer will heal more readily. It has been particularly advised by some investigators in cases in which it is difficult to control night distress. Continuous drip feeding is suggested by some of the advocates of this method of therapy.

Clinically, jejunal feeding has been shown to be of definite value in the treatment of certain intractable types of peptic ulcer. Many diets have been recommended, and even though they contain food substances which are stimulating, they seem to help in the healing of these ulcers. Appell (12), in some recent investigative work in which he made duodenal, jejunal, and gastric fistulas, showed that most foods when placed in the jejunum will cause an increase of the secretory rate of the stomach. Cream and casein consistently stimulated gastric acidity and secretion to a high degree. Apparently, therefore, healing is not dependent primarily on the secretory activity of the stomach in these cases but rather on its retarded motor activity. Unquestionably jejunal feeding allows the stomach considerable rest and it must be this factor which hastens the healing of ulcer in these instances. Appell noted that the pH of the duodenum is higher on jejunal feeding than with any other types of feeding. This increased alkalinity of the duodenal content in spite of increased acidity in the stomach may be a factor in the good results obtained in cases of duodenal ulcer following jejunal feedings. Although this method of therapy may be advisable in certain instances, it is obviously impractical and unnecessary in the average case of uncomplicated peptic ulcer.

Forty-nine per cent of physicians to whom questionnaires regarding ulcer therapy were sent had used duodenal or jejunal feedings in the treatment of peptic ulcer. Twenty-five per cent of these were of the opinion

that this method of treatment had some usefulness in treatment.

COMMENT

In discussing the treatment of peptic ulcer I suggested that it could be divided into three stages; the first of which was the control of distress and the management of complications. During the acute stage of such complications of ulcer it would be dangerous to use vaccines, foreign proteins, synodal or larostidin. Metaphen would certainly be useless and the passing of duodenal tubes might actually cause harm.

The second stage of treatment is the insurance of adequate healing of the ulcer and the application of several physiologic principles is important at this stage. Provision must be made to control the forces of erosion, the healing process being facilitated if gastric acidity, and perhaps peptic activity, are diminished. This is not accomplished regularly by any of the methods of therapy considered in this paper. Gastric motor activity should be protected; duodenal or jejunal feeding aid this, but I can see no reason why this should be favorably influenced by the parenteral methods of treatment or by administration of metaphen. Tissue defenses should be assisted. It is possible that these substances may have some value in fulfilling this therapeutic requirement. Conclusive proof of this, however, is as yet not available.

The third stage of treatment is prevention of recurrences. This is one of the most important tasks of the physician who conscientiously seeks to help the patient with peptic ulcer. Sane methods of living, adequate rest, supplementary feedings, avoidance of infection and nonstimulating diets, are the reasonable ways of accomplishing this. There is no place in this stage of therapy for the newer methods of treatment considered in this paper.

Metaphen may at times be useful as an adjuvant to other treatment of the infected stomach with erosions or ulcers. Mucin therapy is reasonable and may at times help when other methods of treatment fail. Duodenal or jejunal alimentation is occasionally successfully employed to control the symptoms of intractable ulcer. It seems especially useful in the control of night distress.

In the final analysis the parenteral methods of treatment seem to possess no definite claim to merit except in so far as they may initiate or accelerate the healing process of tissue repair. It is doubtful whether this occurs regularly with greater facility than can be accomplished by the older approved methods of ulcer therapy.

It is not my purpose to condemn these various methods of treatment. It is consoling still to have several things to try when the patient is not doing well on pet methods of treatment. In such an instance, however, it is better to concentrate on the method under trial, to work a little more extensively to get the patient to coöperate in treatment, rather than jump from one method to another, which is expensive, destroys the patient's confidence, and in the end usually results in failure.

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DISCUSSION

DR. WALTER L. PALMER (Chicago): I think we owe a real debt of gratitude to Dr. Rivers for this very splendid and lucid exposition of the subject. There is in it nothing with which I care to take exception and therefore I shall not devote any further time to a discussion of the points mentioned by him, but will rather devote it to a consideration of why it is that we have so many methods of treatment for ulcer.

Now, of course, it is obvious that one of the reasons is that we have no method of treatment which is entirely satisfactory. If there were a specific one such as quinine is in malaria, for instance, there would be no argument as to which is the best method of treatment.

Another reason, it seems to me, for the numerous methods of treatment is that the drug houses annually spend large sums of money in order to induce the medical profession to feel that this drug, or that drug, when given intravenously, or some other way, is the finest method of treatment. So, we are all deluged by the detail men who come out and tell us amazing stories. I think we must admit that we physicians as a whole are very gullible men.

Another difficulty is that we have no control group. So far as I know, no one has ever treated a large series of cases in a satisfactory control manner. We know, as Dr. Crohn and others have pointed out, something about the life story of ulcer. We know that there are these spontaneous periods of remission and of exacerbation. Dr. Rivers has adequately considered some of the reasons for the periodicity, but still there is much about it which we do not understand.

A very important fact which is usually overlooked in evaluating results is the role of psychotherapy. We all appreciate the importance of psychotherapy when we are treating the patient, but, in how many instances is it adequately evaluated in a study of results? I might cite, for instance, a patient with a recurrent gastrojejunal ulcer who was unable to tolerate alkalies because of impaired renal function and who did not obtain relief from pain from the various treatments tried. He was told by a wealthy friend that he would be glad to finance a vacation to Europe. On the fourth day out on the boat en route to Europe the ulcer pain disappeared. The patient spent three months touring the continent, eating and drinking everything, attending all of the night clubs in Paris and experienced no more ulcer pain until a month after his return. I am unable to explain this on any other basis than some kind of a psychosomatic reaction. It constitutes further evidence that psychotherapy is extremely important in the evaluation of the results of any type of treatment.

I was reminded yesterday of an article by Maynard written several years ago. Maynard made a pathologic study of the gall bladder removed by the surgeons at operation and then attempted to correlate the changes present with the symptomatic relief afforded by the operation as subsequently reported by the patient. He found that when

stones were present in the gall bladder 84% of the patients reported symptomatic improvement; that when chronic cholecystitis only was present, 65% reported improvement; and that when the removed gall bladder was found pathologically to be normal, 70% of the patients nevertheless reported the operation as clinically successful. We must remember that a major operation such as a laparotomy is a major psychotherapeutic procedure.

Aymen, in Boston, a few years ago reported a study on the effect of psychotherapy in hypertension. He observed the effect of giving ten drops of dilute hydrochloric acid three times per day "seriously and enthusiastically." Dilute hydrochloric acid was selected as the drug to be used because scarcely anyone would have the audacity to say that it could be of therapeutic benefit in any manner except pychotherapeutically. Aymen reported symptomatic improvement in 82% of the cases.

Now with regard to practical methods of treatment for ulcer, I quite agree with Dr. Rivers that the old standard method, particularly the one devised by Dr. Sippy, is the best we have. It is not, as we all know, nearly as successful as it should be, or as we would like to have it. The great difficulty, as has been pointed out by many, including Dr. Sippy himself, is the high night secretion and our difficulty in accomplishing its neutralization. We have studied, as have Winkelstein and others, the height of this secretion during the night in patients with and without ulcer and have found it to be much higher in the ulcer group than in the normal in terms both of free acidity and volume of secretion.

We have tried the Winkelstein drip. I must say it does a better job of neutralizing the free acid throughout the day and night than any other method of treatment which we have employed, except partial gastrectomy. The difficulty of course, is that one cannot keep it up forever. We have continued it for two or three months at a time. We have induced healing of the ulcer, but as Dr. Rivers has pointed out the lesion returns. Nevertheless the method is at times of great value.

Atropin, we feel, has a definite role in therapy because it does decrease the volume of secretion, but, of course, it is not possible clinically to give enough of the drug to completely inhibit gastric secretion.

In conclusion, I take pleasure again in thanking Dr. Rivers.

DR. SANDWEISS (Detroit, Michigan): Dr. Rivers has given us a comprehensive and timely paper on some of the newer methods in the treatment of peptic ulcer. Without a doubt his work will help us in evaluating more accurately the results and indications of some of these therapeutic agents.

About two years ago Dr. S. G. Meyers and I reported our experiences in the treatment of peptic ulcer with a stock respiratory vaccine. We pointed out that although a goodly number of these patients became symptom-free shortly after vaccine therapy was begun, many returned with relapses of ulcer symptoms within one year. Ninety-seven per cent of the patients who became symptom-free developed ulcer relapses within two years.

In my report on forty patients with chronic peptic ulcer treated with histidine (Larostidin), recently published in the Journal, I pointed out that 55% became symptom-free. Of the patients who became symptom-free, 85% returned with relapses of ulcer symptoms within 6 months. This speaks unfavorably for lasting benefits to be obtained from the use of histidine in ulcer therapy.

Dr. Palmer stated that he has failed to find reports on the parenteral treatment of peptic ulcer which included comparative results with control series. I should like to call his attention to the fact that in my report on histidine, previously mentioned, I included not only a control series treated with the standard diet-alkali regime, but also a control series treated with injections of distilled water. I found that the results in these three series of patients were practically the same. I should like particularly to call your attention to the fact that injections with distilled water produced the same immediate results as did injections of histidine (Larostidin).

With reference to the experimental work on histidine mentioned by Dr. Rivers, I should like to add that Drs. Saltstein, Glazer and I have been unable to corroborate the work of Weiss and Aron. In our hands, thus far, peptic ulcers regularly followed the Mann-Williamson operation in dogs even though they had received daily injections of histidine, starting immediately after the operation. I hope to present a preliminary report of this experimental work at the forthcoming meeting of the American Medical Association, Kansas City, showing photographs and photomicrographs of ulcers produced in Mann-Williamson dogs following histidine injections.

I have used four different parenteral methods of treatment in 118 patients with peptic ulcer during 176 ulcer attacks. Approximately 50% of these patients became symptom-free. It is my impression that the psychic factor plays an important role. The physician, in order to justify ten or fifteen or twenty-five injections must of necessity also inject into the patient's mind certain elements favorable to the treatment. He must tell the patient that the parenteral method of treatment is a new treatment, that eminent physicians the world over have reported successful results with its use, that the patient may be able to follow a more balanced diet, etc., etc. These encouraging statements to my mind play a great part in the results obtained.

Here I would like to stress the following facts: Some patients do not respond to any form of medical treatment, whether it be diet and alkalis, mucin, vaccine, Larostidin, Synodal or what not. But, when the psychic problems of these patients are relieved, whether they be environmental difficulties or emotional conflicts, at times an almost miraculous response occurs with or without other therapy. Until more is known about the etiology of peptic ulcer, not only must one manage the ulcer but above all, manage the patient in so far as tensional states are concerned.

DR. ASHER WINKELSTEIN (New York City): Dr. Rivers is to be congratulated on his very able presentation.

The ultimate cause of ulcer is unknown. Three theories are most tenable (1) psychogenic (2) ductless glandular, and (3) inflammatory (infectious?). There is no absolute proof for any of these theories as to the cause of ulcer, but the mechanism by which ulcer is produced seems fairly well-established experimentally and even clinically. It is due either to crises or prolonged hypersecretion of hydrochloric acid, probably vagal in origin, or it is due to the normal or increased acid acting on the tissues rendered vulnerable by an unknown cause. While we cannot attack this unknown factor because we do not know its nature we can attack the known mechanism. The problem of medical therapy in peptic ulcer is to produce that chronic achlorhydria which, as Dr. Alvarez said yesterday, we love to see in our ulcer patients. To date, no medical therapy accomplishes that end. The chief objection to the usual forms of medical therapy is that during the night the stomach is filled with large amounts of concentrated free hydrochloric acid.

Several years ago before this Association I presented a method of controlling the free acid day and night, viz; the continuous intragastric milk drip (alkali is not necessary).

I want to correct Dr. Rivers and many others who have the mistaken idea that this is an intraduodenal or an intrajejunal feeding. It should be emphasized that this is an intragastric milk drip, and this is highly important because the purpose of the treatment is to neutralize the acid in the stomach continuously as it is secreted. If one aspirates samples day or night from these patients, in practi-

cally all the cases there is no free hydrochloric acid and a low total acidity.

Since presenting the method, I have treated over 150 cases and am familiar with the results in another 200 cases so treated by others. The important points about the treatment are as follows: (1) often the patient need only be taught for a few days how to use the milk drip and then be advised to continue it for long periods of time at night at home, (2) it does produce that achlorhydria that we love to see, (3) it is not a heroic method; it is essentially a practical method, particularly for the night, (4) it is successful very frequently when other methods fail.

If it does fail to relieve the patient's symptoms we are probably dealing either with an error in diagnosis, or, a complicated ulcer requiring surgical therapy, or, a profound psychic factor.

I wish to correct one other misconception. One should not speak of a "cure" in chronic ulcer patients: The only cure that I know of for peptic ulcer is partial gastrectomy followed by permanent achlorhydria. Other methods of treatment relieve the patient temporarily and then, sooner or later, the disease recurs.

DR. ALBERT F. R. ANDRESEN (Brooklyn, New York): I consider this paper of the greatest importance.

Such a discussion of the merits of the many newer treatments for peptic ulcer is particularly timely. It is unusual today to see patients with gastro-intestinal symptoms, whether due to ulcer or not, who have not received at least a few of these newer treatments. I have recently seen a patient who had been taking mucin for two years and had had 75 mucin injections, who had no ulcer, but a simple case of sensitivity to milk.

It is only by a consideration of etiologic, pathologic and physiologic factors that we are going to get anywhere in our treatment of ulcer patients, and papers of the type we have listened to this afternoon will do much to clarify the situation. However, one piece of research work, of the utmost importance, has not been given due consideration. This is the work of Lewis Gregory Cole, the successive steps of which have been presented before us in the past four or five years and will be discussed again later today. It was suggested today, and very wisely, that not enough of the researches with newer treatments had been checked by controls. Cole has demonstrated that gastric ulcers, without any specific treatment (or in spite of it) will heal, spontaneously and rapidly. We have demonstrated the same fact in our patients. This rapid healing goes on in spite of the bathing of the ulcer by a hyperacid medium. In older experiments peptic ulcers produced artifically in animals were found to heal so rapidly that they were spoken of as being unlike human "chronic" ulcers, but Cole's work has shown that this makes them like the human ulcers. As a matter of fact we must realize that the rapid healing of gastric ulcer has long been made use of in the differential diagnosis between ulcer and cancer, in that an ulcer which fails to show a disappearance of the crater or a marked diminution in its size is considered malignant.

Cole's demonstration of complete and spontaneous healing of ulcers and the radiographic demonstration that each successive attack of ulcer symptoms represents the occurrence of a new ulcer is capable of demonstration by anyone who, instead of assuming that recurrences are due to the previous ulcer, will again study his patient radiographically. I have seen successive attacks in a patient, due to a lesser curvature ulcer at one time, a duodenal ulcer at another, and a prepyloric ulcer at another, with disappearance of evidences of ulcer at the previous sites or with evidences of slight deformities.

A simple, uncomplicated ulcer is acute, heals spontaneously and requires no treatment. In treating the patient, our main objective is to relieve his symptoms. This is done by frequent feedings, which relieve the hunger contractions causing the pain. The type of feeding is unimportant, except that bland food would seem most logical. Hydrochloric acid does not cause symptoms or prevent healing—I have seen patients do well with the administration of extra hydrochloric acid. The only ulcers requiring specific treatment are complicated ulcers—those having perforated or nearly perforated, with subsequent deformities due to cicatrices, exudates and adhesions, usually requiring surgical intervention, those having bled excessively, necessitating treatment for hemorrhage, and those which were due primarily to malignancy, necessitating early surgery.

The real problem in the treatment of ulcer, as I see it today, is the prevention of the recurrent ulcers—a subject not discussed today.

DR. ANDREW B. RIVERS (Rochester, Minn., closing the discussion): Dr. Sandweiss suggested that in certain instances the use of "larostidin" in the treatment of peptic ulcer was followed by definite improvement. There is evidence to suggest that larostidin might act as a foreign protein and in this way produce beneficial results in some instances where other methods failed to produce prompt results. In our experience, however, larostidin has not given enough promise of permanent benefits to continue its use. In certain instances it might be tried when other, more easily applied methods of therapy fail.

Dr. Winkelstein is to be congratulated upon the efficacy of his gastric drip method in controlling the symptoms of ulcer. In my summary I was not referring to the method of treatment advised by him; I was discussing duodenal and jejunal feedings. Theoretically, all of these methods may have some advantage, and they can be held in reserve to be used in intractable cases which otherwise fail to respond to therapy.

There is a great deal of discussion about the cause of ulcer. An effort is made to find one cause for all ulcers. In all probability peptic ulcer represents not a single disease, but a group of diseases in which not one but a series of causes interact to produce it. Obviously no single cause and no single type of treatment will ever be discovered which will apply in all cases of peptic ulcer. Each case of peptic ulcer is a separate problem which requires individual study and individual processes of therapy.

Cystadenomata of the Pancreas
A Surgical Report*

By

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and

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NEW YORK, NEW YORK

CYSTADENOMATA of the pancreas are among the more infrequent cystic lesions of this organ. Due to the prevalence of drainage and marsupialization as a method of treatment of pancreatic cysts, there are certain instances where an accurate anatomical diagnosis cannot be made from the tissue available. In a series of 19 cases collected from the members of the Chicago Surgical Society, McWhorter found one of malignant papillary adenoma of the pancreas which was thought after examination to have arisen from a cystadenoma. In a longer series of 88 operative and 20 postmortem cases Mahorner and Mattson report two cases of cystadenoma. In view of the border line pathology of many cystadenomas the occurrence of three carcinomas in the series of McWhorter and four carcinomas in those cited by Mahorner and Mattson, the question arises as to whether some of these cases may not have had origin in relatively benign cystadenomata.

The pathology described is quite variable. The majority of the adenomatous cysts are multilocular in character, but this feature is not necessarily present. The cellular structure and microscopic pathology also varies greatly. One type shows pancreatic tissue retaining a fairly normal appearing acinar and ductile structure. The second type commonly described shows a tall columnar epithelium with basal nuclei closely resembling in cellular appearance the cystadenomas of the ovary. Both types may show a certain degree of papillary proliferation of the lining epithelium. The wall in most instances contains fibrous tissue and smooth muscle fibers. The contents of the cyst are generally mucoid in character and contain large amounts of broken down material. There may or may not be pancreatic enzymes in the fluid. Surrounding and walling off the cyst there is a dense capsule of fibrous tissue, undergoing subacute inflammation.

The variations in cellular structure presented by these cysts have led to considerable speculation as to their origin. It is generally agreed that the malposition of certain cells in early embryonic life accounts for their occurrence. There is divergence of opinion however as to which embryonic tissues are the original source.

Felix offers the strayed genital cell theory as an explanation of these lesions. He believes that the cells of the urogenital fold may not arise from differentiated coelomic cells but have their origin from the segmentation cells of early fetal life. These cells leave the region of the cloaca going to the root of the mesentery, and from this point to the urogenital fold. The failure of these cells to reach the urogenital fold is thought to account for the occurrence of these cysts. This view explains readily the occurrence of retroperitoneal dermoid cysts, but Webb-Johnson and Muir raise the point that the absence of all three germinal layers removes pancreatic cystadenomata from this category of teratomatous tumors. Ewing, however, has pointed out that one layer may predominate in such tumors to the almost total exclusion of the other two. A second view somewhat closely allied to the foregoing is that these cysts represent remnants of the mesonephros which have persisted to undergo proliferation during adult life. A third explanation offered is that they represent abnormal budding off from the gut during fetal life.

While none of the embryological mechanisms are entirely satisfactory, the strayed genital cell theory of Felix has the widest acceptance. In view of the variations in pathology it would seem logical to conclude that those showing characteristics closely resembling teratomata or ovarian tissue have their seat of origin in ectopic genital cells of fetal life. On the other hand those showing close resemblance to pancreatic tissue may well have had their origin from some abnormal budding out process of the primitive gut.

The clinical picture presented by cystadenomata differs in no way from other pancreatic cysts. They are essentially a disease of middle life. The most constant symptoms are pain and abdominal enlargement. The pain is generally in the epigastrium or left upper quadrant and does not simulate that of other abdominal conditions. The mass also is in no way distinctive. The size is quite variable and the contour may be smooth or irregular. Mobility is a frequent finding but in the case presented here this was very misleading as at operation the cyst extended into the pancreas on a broad base and was fixed tightly. Masses in the sites commonly occupied must be differentiated from growths in the stomach and colon, renal tumors, circumscribed enlargements of the liver, and other retroperitoneal growths. There are no constantly found associated diseases in this condition, although the case presented here had an accompanying diabetes of seven years duration. There are no diagnostic physical signs and no diagnostic laboratory procedures, the diagnosis if made, being by the process of exclusion of other possibilities.

Marsupialization or drainage of pancreatic cysts is a universally accepted surgical procedure. Judd, however, emphasized the importance of selection of proper cases for excision of the cyst. Examination of the literature reveals excellent results by drainage of the cysts unassociated with epithelial proliferation. However, those cysts which are lined with secretory epithe-

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Approved by the Publications' Committee.

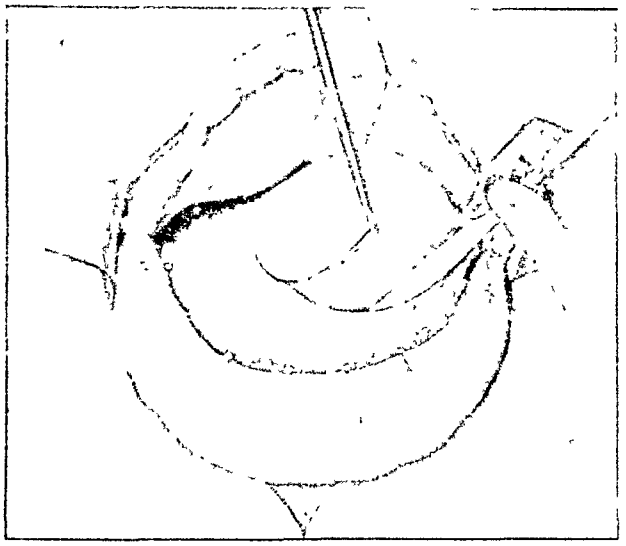


Fig. 1. Subcapsular removal of cystadenomata of pancreas.

lium do not become obliterated in the usual four to six months time, but remain quiescent for varying periods only to open up again. Mahorner and Mattson cite a case having recurrences of multiple cysts for which he was operated upon six times with death five years after the first operation. Speese reports one case of cystadenoma treated by drainage with recurrence ten years after operation. Hamilton reports one case drained in which radiotherapy was necessary to stop the continual discharge from the sinus where drainage had been instituted. In view of these facts excision, wherever technically possible, should be the surgical goal in the treatment of these cases.

Malignant degeneration with an extension to the surrounding tissues through the inflammatory fibrous wall makes it impossible to remove the growth. An excision of the cyst by separating the outer cyst wall from the pancreatic structure was considered impossible in the case presented. The density of the junction of cyst to surrounding structure together with the inability to establish a line of cleavage at this point made the operation as shown in Fig. 1 seem to be the only possible method for removal. Had the cyst been malignant and extension to the inflammatory capsule taken place before operation the entire growth would not have been removed by this method.

The method as shown is very similar to the common subserous removal of the acutely inflamed gall bladder. The wall of the cyst was obviously thick and edematous presenting very much the same picture as the serous surface of an acutely inflamed gall bladder.

An incision into the wall of the cyst about one-quarter inch from the pancreatic tissue margin was made half way around the inferior border of the cyst. One must judge the thickness of the cyst wall and carry the incision into the wall only sufficiently to establish a line of cleavage. Grasping the upper margin of the line of incision in nosed clamps enables traction to be placed on the cyst. The lower margin is bluntly forced away from the cyst and a line of cleavage established. As soon as the line is well established, the dissecting finger carries on as the cyst is retracted forward and upward. The dense fibrous tissue yields

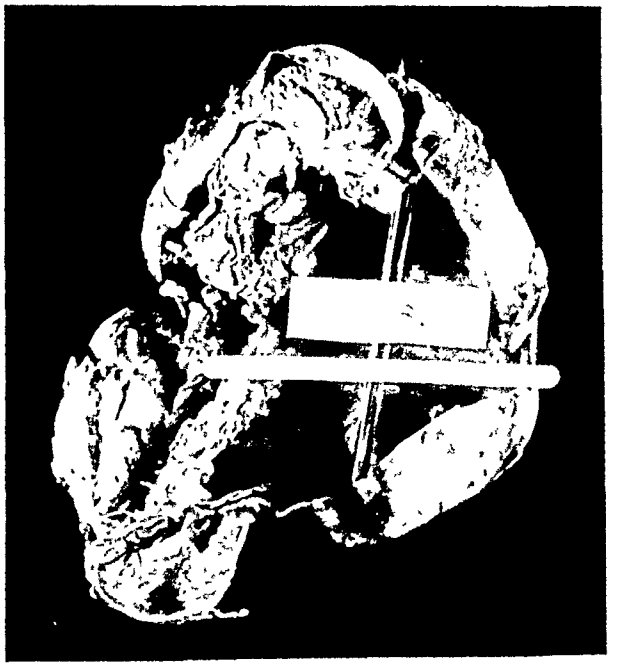


Fig. 3

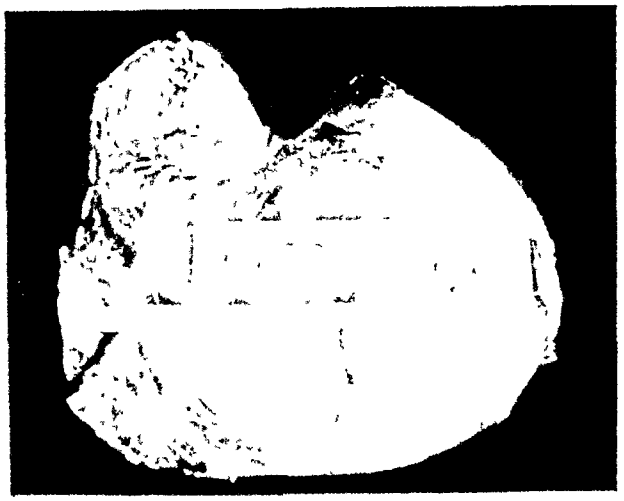


Fig. 2

to splitting because of the edematous nature of its structure.

In the fibrous tissue wall there was encountered toward the mid-line several venous sinuses that bled profusely just before the cyst was lifted out. Those in the margin of the cyst wall were clamped but could not be tied because of the dense fibrous tissue. The clamps were left in place, the center of the cavity was packed with gauze. The clamps and packing were brought up through the opening in the gastro-colic omentum and left protruding through the center of the incision.

On the fourth day post-operative the clamps were unlocked and as no bleeding occurred they were removed the following day. Hemorrhage was rather profuse at operation and blood transfusion for secondary anemia was performed the week following operation. The gauze packing was removed on the ninth day with the patient in the operating room so that repacking could be done in case of bleeding. No further packing

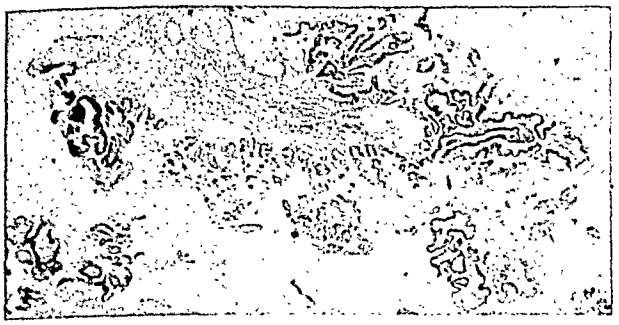


Fig. 5

was necessary and the wound healed by secondary union. The patient was discharged from the hospital on the 24th post-operative day.

CASE REPORT

R. O., a 48 year old Jewish housewife, complaining of mild generalized abdominal pain of an aching character for eighteen months. This was unrelated to meals and was unassociated with any other symptoms. One year before admission she was in another hospital where a mass was found in the left upper quadrant and operation advised. This was refused and following discharge she was well except for weekly attacks of pain.

She had been a mild diabetic of seven years duration and had been easily controlled by dietary management. Two months before admission she began to complain of paresthesias of the extremities and at this time urinalysis showed glycosuria. As these symptoms continued with ambulatory treatment she was advised to enter the hospital for a general checking over of the diabetic situation.

Physical examination showed a well nourished obese woman of middle age, who had no physical abnormalities other than those found in the abdomen. In the left upper quadrant there was a hard, irregular, freely movable, non-tender mass about 10 by 8 cm. in size. The mass moved with respiration and on percussion a dull note was obtained over it.

Laboratory findings: A flat plate of the abdomen showed an ovoid mass 12 cm. in diameter occupying the left upper quadrant, distinctly demarcated from the spleen and the left kidney. There were nodules present about the periphery of the mass and faint calcareous deposits were noted on the superior and medial sides.

The blood picture was normal showing R.B.C. 4,670,000,

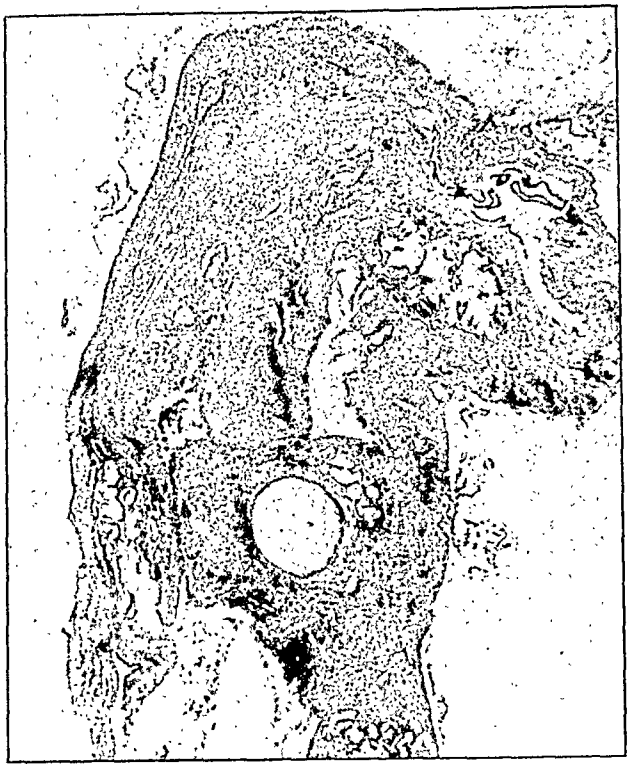


Fig. 4

Hemoglobin 88 per cent, W.B.C. 7500, with normal differential. No parasites were found in the stained smear.

Chemical examination of the blood showed non-protein nitrogen of 36.6 mg. per 100 c.c., urea nitrogen 13.5 mg. per 100 c.c., sugar 162 mg. per 100 c.c., cholesterol 270 mg. per 100 c.c., and a CO_2 combining power of 67.3 volumes per cent.

The blood Wasserman was negative.

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IN MEMORIAM

John Bryant*

By

FRANKLIN W. WHITE, M.D.

BOSTON, MASSACHUSETTS

It is hard to lose our older men; it is doubly hard to lose one of our younger, vigorous men, in his prime.

John Bryant was born on our New England seacoast at Cohasset, Massachusetts, of old New England stock. He graduated from Harvard College and Harvard Medical School. He was a sailor, which always endeared him to me, with a spirit of adventure, and delighted in long cruises in small boats. He spent two years abroad and his research work in Vienna bore

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fruit in some of his most quoted papers on the measurements of the intestines. He had a long military service during the war, beginning with the rank of Captain and ending with the rank of Major. He was greatly interested in problems of convalescence and wrote valuable papers on this subject, as well as a book entitled, "Convalescence: Historical and Practical" (1927).

He was a consultant of the Burke Foundation for Convalescents, New York City, and Medical Assistant in Problems of Convalescence at the Massachusetts General Hospital. He was also Assistant Physician at the Robert Brigham Hospital in Boston.

John Bryant's genial, happy disposition, his tact and kindness, endeared him to his many patients and enabled him to work wonders with that difficult group of asthenias affected with gastro-intestinal symptoms. He has written a series of valuable papers on the Intestinal Neuroses.

As you all know, John Bryant was a devoted secretary to our Association for a period of four years (1923 to 1926, inclusive), always painstaking and thorough, doing everything possible to advance the interests and standing of our Association. The careful revision of our Constitution and By-Laws in 1921 was entirely his idea and largely carried out by him. He was a valuable member of our Council and later was elected President. It was a tragedy that this honor came at a time in his life when illness prevented him from presiding at the Annual Session.

The going of John Bryant takes from our Association an active, valuable, and much loved member.

Lafayette Benedict Mendel: An Appreciation*

By
VICTOR C. MYERS, Ph.D., D.Sc.
PALA ALTA, CALIFORNIA

Lafayette Benedict Mendel was born at Delhi, N. Y., February 5, 1872, the son of Benedict and Pauline (Ullman) Mendel, highly respected citizens of Delhi. The town of Mendel's birth was very proud of the record he subsequently made. He was appreciative of this evidence of affection, and continued to return to Delhi for his summers until overtaken by his tragic fatal illness two years ago. He died on December 10, 1935.

Lafayette Mendel's interest in physiological chemistry was aroused by Professor Russell H. Chittenden under whom he took his Ph.D. degree in 1893 at the early age of 21. After serving as an instructor for two years he spent the two following years in various laboratories in Germany on leave of absence, then returned to Professor Chittenden's department at Yale and advanced through the various grades to a full professorship in 1903 and to the newly created Sterling Professorship of Physiological Chemistry in 1920.

Professor Mendel received nearly every honor which could be conferred upon him, a partial list of which will be given. He was a member of the National Academy of Sciences, the American Philosophical Society, an Active Member of this Association from 1907-1930, an Honorary Member since 1930, and numerous other scientific societies both here and abroad. He served as President of the American Society of Biological Chemists and the American Institute of Nutrition. He was a member of the Council on Pharmacy and Chemistry, and of the Committee on Foods of the American Medical Association. He served the U. S. Government in many advisory capacities during the World War, and also represented it on the Interallied Food Commission abroad. He was a member of President Hoover's White House Conference on Child Welfare and Development. He served as an Editor of the *Journal of Biological Chemistry*, *Journal of Nutrition*, *Chemical Reviews* and was a frequent unofficial contributor to the editorial pages of the *Journal of the American Medical Association*. He gave the Herter lectures at New York University, the Hitchcock lectures at California, the Schiff lectures at Cornell, the Cutter lectures at Harvard and twice lectured be-



LAFAYETTE BENEDICT MENDEL

*Presented before the Thirty-Ninth Annual Session of the American Gastro-enterological Association, Atlantic City, N. J., May 4-5, 1936.

fore the Harvey Society. In 1934, the Chemists' Club of New York awarded him the Conne medal for outstanding chemical service to medicine. He received the honorary degree of Sc.D. from Michigan and Rutgers and that of LL.D. from Western Reserve University. In his own University he served as a member of the Governing Board of the Sheffield Scientific School and of the Board of Permanent Officers of the Graduate School and School of Medicine. On his sixtieth birthday his students and friends presented his portrait to the University, the former contributing to an anniversary number of the *Yale Journal of Biology and Medicine* which was dedicated to him.

Despite these many honors, Mendel's claim to greatness probably rests more upon his remarkable ability to train others than upon any other quality. I am sure that he took greater pride in this than anything else. When a student undertook a research problem, Mendel did not select some topic in his own field of research, but tried to help the student pick a problem which might be the beginning of the student's own life work. He was most unselfish in this as he was in the manner of publication. By his own unique methods he aroused and stimulated the student during the investigation. Above all he taught the student to think for himself. Good work received suitable recognition, and although mistakes and errors were not directly criticized, they never missed his eagle eye. Mendel kept in constant touch with his students after they left his laboratory, and very few there were who did not frequently turn to him for advice, which was always given promptly and cheerfully. He wrote a beautiful and very legible hand and for many years took care of his personal correspondence in this way. It was a great incentive to receive one of those witty and stimulating letters from master and friend.

Ninety-two students received the Ph.D. degree under his guidance, and these may be found actively trying to follow the example of their teacher in some of the most representative institutions of this country.

Although, in Professor Mendel's later years, nutrition may be considered his chief interest, he was always much interested in gastro-enterology, perhaps in part because of his training under Chittenden and Heidenhain. Numerous investigations in his laboratory, particularly in the earlier years, touch upon almost all phases of digestion and absorption. He was also much interested in the clinical application of this work and was frequently consulted by gastro-enterologists. As a student, I recall his referring to the work of Meltzer, Hemmeter and Einhorn, and to this Association.

For more than twenty years, however, his interest largely was in the field of nutrition. In 1919 he presented a paper before this Association on "Food Factors in Gastro-enterology," in which he stated: "It seems to me . . . that a discipline which relates to the normal and pathological conditions of the digestive organs cannot fail to find some interest in the *rôle* of the foods, for the transformation and transport of which these organs exist, or in the phenomena of nutrition for which the function of digestion is an indispensable preparation." In this way he related most of the work of his later years to gastro-enterology.

Few men exerted so wide an influence as Lafayette Mendel; very few have trained so many to "carry on" when they are gone. This Association may well be proud to have had Mendel as both an Active and an Honorary Member.

Harlow Brooks*

By

WILLIAM GERRY MORGAN, M.D.
WASHINGTON, DISTRICT OF COLUMBIA

Dr. Harlow Brooks was born at Medo, Minnesota, on March 31st, in 1871. He received his preliminary education in the High School of Medo, and later graduated from the University of Oregon. In 1895 he received the degree M.D. from the University of Michigan School of Medicine, and from the same School received the honorary degree of M.Sc. in 1930. He took post graduate study at the University of Freiberg, and at the Polyclinic in Munich. He was Assistant Demonstrator of Anatomy at the University of Michigan School of Medicine in 1895; Instructor of Histology and Embryology, Bellevue Hospital Medical College, 1895-98; Research Fellow in Bacteriology, New York State Hospitals, Pathological Institute, 1887-1920; Professor of Clinical Medicine, New York University Medical College, 1922-1929.

At the time of his death Dr. Brooks was Emeritus Professor of Clinical Medicine, New York University Medical College; Visiting Physician, Bellevue Hospital; Consulting Physician, New York City, French, New York Polyclinic, Union, Fifth Avenue, Hackensack, New Jersey, Beth Isreal, Greenwich, Mount Vernon, Saint John's, Southside (Bay Shore) Flushing, Jamaica, Bronxville and Montefiore Hospitals, Hospital for Joint Diseases and Norwegian Lutheran, Deaconess's Home and Hospital. His World War record: Major, Lieut. Colonel and Colonel, M.C.U.S.A.; Chief of Medical Service Base Hospital, Camp Upton; Chief Consultant in Medicine First Army Corps, A.E.F.; Senior Consultant in Medicine, Second Army Corps, A.E.F.; Awarded Distinguished Service Medal, General Citation. He was a member of the American Legion and of the Association of Military Surgeons.

He was a member of the Phi Alpha Sigma fraternity; Member of the Harvey Society, Society of Experimental Biology and Medicine, Association of American Physicians, American Medical Association, American Gastro-enterological Association, Medical Society of the State of New York, New York County

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Medical Society, and the American College of Physicians. He was elected Fellow of the American College of Physicians at its first regular meeting held in New York in December, 1916. He was elected President in 1923 in which capacity he served for two years. In 1925 he was elected to the Board of Regents where he served for three years; in 1929 he was elected to the Board of Governors on which he served for two years. He also served on various committees and gave generously of his time and energies to the work of the College.

Dr. Brooks was a prolific writer and published many monographs and special articles on medical and biological subjects. He was the Editor of Lippincott's Everyday Practice Series.

He was keenly interested in animal life, exploration, mountaineering and was an honorary Fellow in the New York Zoological Society and a member of the Explorer's Club, Adventurer's Club, and the Camp Fire of America.

Dr. Brooks was one of the outstanding diagnosticians of his time and was called in consultation as frequently probably, as any other doctor in the United States. He was looked upon as an authority in diseases of the circulatory system. He was often referred to as the "doctors' doctor," being constantly sought by his brother practitioners in cases involving their immediate families, among whom he was known as the "Beloved Physician."

Few physicians of his time gave so generously of their services to the poor.

As a young pathologist, Dr. Brooks collaberated with Dr. William Welch at Bellevue Hospital in advanced research work that resulted in the discovery of the bacillus named after Dr. Welch which is responsible for the disease commonly called "gas bacillus" infection, and which, by a curious coincidence was the cause of Dr. Brooks' own death.

One of the contributing factors which enabled Dr. Brooks to maintain his enthusiasm for his profession and for life in general was his devotion to his hobbies which were very varied. He was a skilled musician and a collector of outstanding works of art, as well as being an anthropologist of note. His collection of Indian relics surpassed any similar private collection in the world; it contained some specimens not to be found in any other collection.

Probably his great physical stamina was due, in part at least, to his love for fishing and hunting, in each of which he was an outstanding expert. Often Dr. Brooks would remark that he gladly devoted ten months each year to the pursuit of his profession but retained two months to seek recuperation and happiness in the great open spaces.

One of the outstanding characteristics of this great physician was his genius for friendship. His friendship was a living vital force upon which rested profound gratification and innermost happiness. When Dr. Brooks bestowed his friendship it was for the duration of life. He was truly catholic in these friendships which were confined to no one profession or social stratum. Caring little for individual accomplishments, Dr. Brooks demanded honesty, frankness, and I was about to add, loyalty in his friends. However, since loyalty is the quintessence of true friendship, it may be omitted.

I have somewhat stressed this phase of Dr. Brooks' character because to him it was the dominating influence of his life, and also, because in these times of emotional upheaval and cross purposes the gift of true friendship is a God-given attribute which is all too rare.

And so, from our midst, has been taken this great physician, this talented gentleman, this indefatigable worker, this scientist of renown, this man of many enthusiasms, of loyal friendships, of kindly heart and broad sympathies—gifted in so many ways and with so many talents that the world, indeed, is richer for his having lived in it. Those who had the privilege of close association with Harlow Brooks will carry in their hearts ever the memory of his cheering and inspiring presence and the light of his Christian spirit.

Henry Wald Bettmann*

By

LEON SCHIFF, M.D.
CINCINNATI, OHIO

Dr. Henry Wald Bettmann, senior member and President of the American Gastro-enterological Association, died on December 4, 1935, of coronary artery disease.

Dr. Bettmann was born in Cincinnati, Ohio, on January 14, 1868, the son of Matilda Wald and Bernhard Bettmann. In 1887 he received his A.B. degree from the University of Cincinnati and was elected to Phi Beta Kappa. Three years later he was graduated, with honorable mention, from the Medical College of Ohio. After a year's interneship in the Cincinnati General Hospital, he spent two years in graduate study in the clinics of Berlin, Prague and Vienna.

In 1893 he was given the appointment of "Curator of the Laboratory" at the Cincinnati General Hospital. While serving in this capacity he originated the first city-wide service for the bacteriological diagnosis of diphtheria. At the same time, with the help of several colleagues, he opened a course in clinical laboratory methods for practitioners. He was appointed pathologist to the Cincinnati General Hospital in 1894, which position he held until 1907.

Early in his career, Bettmann's interests began to lean toward the field of gastro-intestinal diseases. In 1903 he received the prize for a monograph on studies of the shape and position of the stomach. In 1904 he was elected Second Vice-President of the American Gastro-enterological Association and served as President during the years of 1905 and 1906.

*Delivered before the Thirty-Ninth Annual Session of the American Gastro-enterological Association, Atlantic City, N. J., May 4-6, 1936.

Dr. Bettmann made numerous contributions to the subject of diseases of the digestive tract and was particularly interested in the problem of so-called chronic appendicitis with particular reference to the pit-falls in the diagnosis of this condition as evidenced, for example, by the failures following surgical treatment. He was, up until the time of his death, engaged in a large practice much of which was consulting in character.

He wrote the chapters on Diseases of the Liver and Diseases of the Intestines for the George Blumer edition of *Forcheimer-Billings Therapeusis of Internal Diseases*. He wrote the section on Diarrhea for Nelson's *Loose-Leaf Medicine* and the section on Examination of the Feces in Tice's *System of Medicine*.

Dr. Bettmann was a friend of the younger medical man and would constantly encourage him in his undertakings. He was a man of diversified interests. His knowledge of literature, both ancient and modern, was profound. Both the fields of poetry and philosophy were his in which to wander and a remarkably tenacious memory made what he read his own possession. He was a chess enthusiast of the highest order; he delighted in setting and solving the most intricate problems. His was a mind which lent itself naturally to a culture of uncommonly wide extent. Endowed with a delightful sense of humor, his qualities made him a colleague to be loved and cherished; his humanitarianism and ability, one to be admired.

His passing represents a distinct loss to this Association.

George Washington McCaskey*

By

WILLIAM GERRY MORGAN, M.D.
WASHINGTON, DISTRICT OF COLUMBIA

Through the death of George Washington McCaskey in Fort Wayne, Indiana, on December 30th, 1935, the American Gastro-enterological Association lost one of its earliest and most distinguished members.

Dr. McCaskey was born in Fulton County, Ohio, November 9, 1853. He was graduated from the Jefferson Medical College in 1877 and in 1880 from the University College of London, England. Upon his return to his native land he established his practice in Fort Wayne, Indiana, where he continued his life work up to the time of his death. He retired from clinical work seven years ago, to devote himself to writing and to research.

By his untiring devotion to the pursuit of knowledge in his chosen profession, Dr. McCaskey won a high place as a diagnostician and clinician, and was a recognized authority in diseases of the alimentary tract.

Dr. McCaskey was a prolific writer and his contributions to medical literature were numerous and valuable.

In 1910, Dr. McCaskey was a delegate to the International Medical Congress at Madrid, Spain, at which he delivered a noteworthy address.

Dr. McCaskey had several honorary degrees conferred upon him in recognition of his professional attainments, among which were Ph.B. in 1881 and M.A. in 1884, both by the DePauw University.

Dr. McCaskey by his broad vision, keen judgment and wise council won the confidence and esteem of those with whom he worked for so many years.

Be it Resolved: That we, the American Gastro-enterological Association express our deep sorrow for the loss of this true physician and wise counselor.

Be it Further Resolved: That these resolutions be made a part of the permanent records of this Association, and a copy be sent to the surviving members of Dr. McCaskey's family as a token of the high regard and esteem in which he was held by the members of the American Gastro-enterological Association.

*Delivered before the Thirty-Ninth Annual Session of the American Gastro-enterological Association, Atlantic City, N. J., May 4-5, 1936.

Annual Abstracts of Proctologic Literature, 1935-1937

By CHARLES E. POPE, M.D., Evanston, Illinois

INTRODUCTION

IN the performance of my duty in the review of the Proctologic Literature for the past year, it was immediately evident that the task was nearly Herculean and apparently never ending. That satisfaction that comes with the exhausting completion of a single subject for review is not the reward of the compiler of the Proctologic Literature for this Society. To do that is a physical impossibility and with the added interest given our specialty and the increasingly large numbers of contributions, coupled with the importance of having a careful analysis of the literature on the multitude of related subjects, there might be some question as to the wisdom of delegating the work to a single member of the Society in the future.

As it has been with my predecessors, additional help always has been necessary from librarians and from abstractors for both foreign and domestic abstracts; and each one has mentioned that, though a voluminous report was given, nevertheless it was by necessity many hundreds of articles less in the Transactions than the number actually reviewed. My respectful admiration and appreciation of past reviewers rapidly mounted at the start of this work last year.

Whereas this is merely offered as a suggestion for your future consideration one definite change was made following the suggestion of the secretary,

to carry the review to the present year and not beyond. This year's review therefore commences in May, 1935, and carries to January, 1936, whereas next year's review should be wholly a 1936 review.

GENERAL

Dr. Frank Smithies through the American Journal of Digestive Diseases and Nutrition as his spokesman has written one of the finest editorials on our specialty that the writer has had the privilege of enjoying. The just prominence and attainments of the author adds greatly to the importance of the article, and the article itself does much to further proctology.

Cecil Gaston emphasizes the need for the advancement of proctology and illustrates the excellence of that department in the South Highlands Infirmary in Birmingham.

Gaston, C. D.: The Department of Proctology. South Highlands Infirmary, Birmingham, Ala., Oct., 1935.
Smithies, F.: Proctology: A Specialty, and Its Influence Upon This Journal's Publication Policy. *Am. J. Dig. Dis. and Nutrit.*, 2:635, No. 10, 1935.

ADENOMAS

This subject is also discussed in papers on related subjects and in papers on electro-coagulation.

Fansler discusses advanced as well as early cases. Lesions visualized within the last 25 cm. of bowel are the pedunculated adenomas and the flat or button type which are particularly prone to malignancy. The pedunculated may be fibrous and therefore non-malignant or may be villous or papillary.

Geschickter in a review of 178 cases of benign tumors of the gastro-intestinal tract found a total of 90 adenomas of which 10 were colon and 55 rectal. In the malignant group, however, this relative proportion changed for in a series of 1472 malignant tumors, 250 were colon and 370 were rectal.

Lockhart-Mummery believes that the simple adenoma is merely a stage in the development of malignancy. In 50 cases a recurrence was present in half of the cases. The author believes that gene mutation occurs in a cell nucleus resulting in excessive reproduction.

Mandillon and *Georget* believe that diffuse intestinal polyposis and the localized form have an irritative infectious origin but an etiology and pathogene-is still uncertain and that whether they constitute two different degrees of the same affection or two different diseases present knowledge does not permit to say.

Nystrom reports 7 cases of diffuse polyposis of the rectum and colon. Four cases died from cancer and 2 pairs occurred in brothers.

Oppolzer reports a case of papillomatous polyps in the cecum which recurred following a cecal fistulectomy performed 2 years following appendectomy. Chronic inflammatory irritation from long pus discharge and intramural resorption played a definite part as a causal factor.

Rankin reviews 11 cases of adenomatosis 6 of which were previously reported. The present 5 were complicated by ulcerative colitis. Discusses the surgical aspects. One case had fulguration and a reestablishment of bowel continuity by operation.

Bargen, J. A., and Dixon, C. F.: Hereditary Polyposis of the Large Intestine. *Proceedings of the Staff Meetings of the Mayo Clinic*, 10:648, Oct. 9, 1935.
Fansler, W. A.: Diagnosis and Prognosis of Epithelial Tumors of the Large Bowel. *J. A. M. A.*, 105:167, July 20, 1935.
Geschickter, C. F.: Tumors of the Digestive Tract. *Am. J. Cancer*, 25:130, Sept., 1935.
Lockhart-Mummery, J. P.: Relationship Between Adenomas and Cancer of Large Bowel. *Lancet*, 1:1149, May 18, 1935.
Mandillon and Georget: (Diffuse General Polyposis of the Bowel). *Rev. de Chir.*, 54:238, March, 1935.
Nystrom, T. G.: Contribution to Knowledge of Diffuse Polyposis of Large Intestine. *Finska läk.-sällsk. Handl.*, 77:619, Oct., 1935.
Oppolzer, R. R. V.: (Polyps in Large Intestine) Ein Beitrag Zur Polypenentstehung im Dickdarm. *Arch. f. Klin. Chir.*, 182:152, March 4, 1935.
Rankin, F. W.: Colectomy for Adenomatosis and Pseudopolyposis: Report of Five Additional Cases. *Ann. Surg.*, 102:707, Oct., 1935.

AGRANULOCYTOSIS

Küpper reviews 327 cases from 43 different observers—German, English, French, American, and Norse, and includes sixteen of his own cases and concludes that the disease is 3 times as frequent in the female, occurs most frequently between 30 and 60, shows an average mortality of 75% (94% of authors own cases), and that therapy is of little value.

Kracke and *Parker* review the literature and conclude that amidopyrine, dinitrophenol, and closely related drugs are responsible as etiologic factors.

Norris reviews 76 cases. The mortality was 79% and the average age 41.

Kracke, R. R., and Parker, F. P.: Agranulocytosis: Etiology, Diagnosis and Treatment. *South. M. J.*, 28:911, Oct., 1935.
Kracke, R. R., and Parker, F. P.: Relationship of Drug Therapy to Agranulocytosis. *J. A. M. A.*, 105:1017, Sept. 21, 1935.
Küpper, A.: (Nosology and Statistics of Agranulocytosis). *Klin. Wchnschr.*, 14:1684, Nov. 23, 1935.
Norris, J. C.: Pathology of Agranulocytosis. *South. M. J.*, 28:501, June, 1935.

AMEBIASIS AND PARASITIC INFECTIONS

AMEBIASIS. Amebiasis showed itself to be endemic and sporadic in occurrence during 1935. Increased recognition of the disease in other stages than its dysenteric form is encouraging. Experimental work has given interesting and apparently very practical and constructive knowledge of the endamoeba histolytica. Therapy is little changed from previous methods and favors combined medication.

EXPERIMENTAL AND INCIDENCE. *Spectors* found that freshly isolated pathogenic organisms in man when inoculated with endamoeba histolytica in the kitten increased both the severity and the extent of ulcerations so produced. This was most marked with the hemolytic streptococci and occurred likewise but to a lessened extent with pneumococcus Types I and III and a green producing streptococcus from ulcerative colitis. When, however, prolonged cultivations of the endameba histolytica and hemolytic streptococcus were used the mortality and the degree of ulceration produced experimentally was markedly reduced. The work was done in careful detail and well controlled.

Nauss suspects that intestinal bacteria play an important role likewise inasmuch as his experimental inoculation of new cultures of endameba histolytica alone or with hemolytic b. coli in kittens were most apt to produce infection. He suspects therefore that only grossly contaminated water and food produce epidemics as in Chicago and that carriers do not play an important part, but that in the individual cases occur mainly because of a depressed resisting power of the gut. The author reviews the incidence of protozoa including endamoeba histolytica in 850 routine examinations and by sigmoidoscopy as well as by removal of material proctoscopically in 270 cases. Repeat examination increased the incidence of endameba histolytica 50% which for food handlers should be 9-10%.

Stites agrees with this incidence and from personal observations states the incubation period whereas quoted as 10-100 days may be as early as 48 hours.

Wenrich, *Stabler* and *Arnett* in a study of 1060 students from 1930-1933 report 4.1% harbor endameba histolytica whereas 34.5% harbor protozoa. Permanent slides gave more positives than wet preparations. Stools were used.

COMPLICATIONS. *Anderson* condemns the use of emetin for other than in amebic hepatitis or abscess or where complications requiring surgical intervention necessitate it due to danger of permanent cardiac damage. Advocates local excision of granulomas or rectal pathology (ulcer) if such exist. States refractory cases occupy 10% of his cases and advocates appendicostomy for continuous irrigations of the colon. His discussants notably William Boack did not agree with him regarding the non-use of emetin.

Guichard and *Paponet* report a case showing inflammatory polyposis. Biopsy from an apparent "rectal adenoma" confirmed the clinical impression. The neoplasm disappeared on emetin and Stovarsol treatment.

Meleney and *Meleney* report an unusual case of gangrene of the buttocks, perineum and scrotum due to the lytic action of the endameba histolytica and not accompanied by other bacterial invasion. Skin graft was necessary.

TREATMENT. *Brown* and *Magath* in an excellent review of amebiasis state that the complement fixation test is as

yet too complicated for routine use and that cultural methods offer a good method excepting that characteristics of the cultured amebae are not well enough known. Emetin gr. 1 subcutaneously twice daily for three days is commenced with treparsol 0.25 gm. three times daily for 4 days. Three such courses are given at ten day intervals. Yatren three grams daily for a week followed by emetin and treparsol if necessary and repeated in a week is given for recurrence.

O'Connor and *Hulse* report excellent results in the use of iodoxyquinolin sulphonic acid (anayodin) in 152 cases. They give 4 pills three times daily for 8 days.

PROTOZOAL INFECTIONS OTHER THAN ENDAMEBA HISTOLYTICA. *de Paula E. Silva* report 22 cases of giardiasis obtained from bile in biliary drainage. Symptoms due to duodenum and biliary tract were present.

Gabaldon experimented on rats with strains of balantidium coli. No reference to human cases is made.

Gachlinger found lambliasis in vegetative form 70 times and their cysts 32 times in examining 318 cases of chronic colitis. Endameba histolytica was found in vegetative form 4 times and encysted 11 times in the same 318 cases. The frequency of lambliasis explains the frequency of favorable results in the use of arsenical treatment of cases.

Savy et al cite a case of hemorrhagic rectocolitis in which the feces showed ascaris eggs. Intravenous thiosulphate caused complete cure.

Anderson, H. H.: Amebiasis: Important Aspects of Its Treatment. *Calif. and West. Med.*, 42:340, May, 1935.

Brown, P. W., and Marath, T. B.: Amebiasis Diagnosis, Prevention and Treatment. *Minnesota Medicine*, p. 515, Aug., 1935.

de Paula E. Silva, G. E.: A Clinical Review of Giardiasis; Twenty-two Cases Observed During Study of 572 Private Patients. *Am. J. Digest. Dis. and Nutrit.*, 2:350, Aug., 1935.

Feller, A. E., and Greene, J. A.: Amebiasis Report of Six Cases. *J. Iowa State Med. Soc.*, 25:437, Aug., 1935.

Gabaldon, A.: Balantidium Coli: Quantitative Studies in Experimental Infections and Variations in Infectiousness for Rats. *J. Parasitol.*, 21:386, Oct., 1935.

Gaehlinger, H.: Growing Importance of Lambliasis in Etiology of Colitis. *Paris Med.*, 2:149, Aug. 31, 1935.

Guichard and Paponnet: (Rectosigmoid Pseudocancer of Amebic Origin). *Arch. d. Mal. de l' App. Digestif.*, 25:460, May, 1935.

Meleney, F. L., and Meleney, H. E.: Gangrene of the Buttock, Perineum and Scrotum Due to Endamoeba Histolytica. *Arch. Surg.*, 30:980, June, 1935.

Nauss, R. W., and Salinger, M. H.: Amebic and Other Intestinal Protozoal Infestations in Representative Groups of New York City. *Am. J. of Public Health*, 25:819, July, 1935.

O'Connor, F. W.: Dissemination of Amebiasis. *Arch. Int. Med.*, 55:997, June, 1935.

Savy, P., Chapuy, A., and Girard, M.: (Hemorrhagic Recto-colitis of 15 Years' Evolution; Recovery Following Desensitizing Therapy with Sodium Thiosulphate). *Lyon Med.*, 156:404, Oct. 6, 1935.

Spector, B. K.: Changes Produced in Intestines of Kittens by Endameba Histolytica, with and without Certain Added Bacteria. *Am. J. of Hyg.*, 22:366, Sept., 1935.

Stites, F. M.: Amebiasis. *Kentucky Med. J.*, 33:220, May, 1935.

Wenrich, D. H., Stabler, R. M., and Arnett, J. H.: Endromeba Histolytica and Other Intestinal Protozoa in 1060 College Freshmen. *Am. J. Trop. Med.*, 15:331, May, 1935.

ANATOMY

Hiller states that the confusion existing concerning the white line of Hilton is that post mortem findings are not as in vitro, that it is identical with the pecten of Stroud. Because of poor vascularity it shows as a white line representing fibrous tissue deposit beneath the uncornfied epithelium at the termination of the muscularis mucosae.

Tucker and *Hellwig* give an excellent contribution to our knowledge of the anal ducts based on a study of the anal histology in the dog, cat, guinea-pig, rabbit, and chicken and on longitudinal sections of six human embryos. This comparative study as well as the study of pathological specimens of the prostate and paraurethral glands showed that the anal prostate and paraurethral ducts are hemologous structures, develop in the embryo at the same time and arise from the anal intermediate zone and urogenital sinus respectively, which in turn are cloacal in origin. The anal ducts are vestigial remnants of the larger glands seen in the intermediate zone of the anal canal as a complex gland in the dog, pig, and rabbit, and a cloacal gland in the chicken. Pathologically the ducts are apt to harbor gonococci as is the case in the prostate and paraurethral glands.

Hiller, R. I.: Anal Anatomy with Reference to the White Line of Hilton and the Pecten of Stroud. *Ann. Surg.*, 102:81, July, 1935.

Tucker, C. C., and Hellwig, C. A.: Anal Ducts: Comparative and Developmental Histology. *Arch. Surg.*, 31:521, Oct., 1935.

ANESTHESIA

Lundy discusses the extent to which the inexperienced person may be justified in using certain anesthetic agents and reviews these drugs from this viewpoint.

NEW ANESTHESIAS. *Lundy* describes a new form of anesthesia where two or even three times the usual 30 c.c. of a 1% procaine solution may be injected into the caudal canal. It may be reinforced with second sacral foramina injections. Campbell states 70 cases have been tried at the Mayo Clinic since January 1, 1935, of which 6 were anal or rectal. 30 minutes or more is required for anesthesia. Sacral anesthesia was satisfactory in 96% of 10,960 cases at the Mayo Clinic from 1924 to 1934. Lundy in his discussion includes an extensive and complete bibliography on the subject.

Lundy describes two new barbiturates for short profound general anesthesia for use intravenously. Operations lasting 10 to 15 minutes are satisfactory for these drugs. The drugs are termed Barbiturate A and B, the former being more profound is the more satisfactory and is sodium ethyl 1 methyl butyl thiobarbituric acid. The drug is termed



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Kellogg and Mettier (Arch. Int. Med., 58:278-Aug., 1936) have demonstrated that "alkalinization of the upper part of the gastro-intestinal tract interferes with the utilization of dietary iron for the synthesis of hemoglobin," and delays recovery from the anemia.

Creamalin, a specially prepared amphoteric colloidal cream of aluminum hydroxide, is not an alkali and therefore will not produce an alkalinization of the upper part of the gastro-intestinal tract.

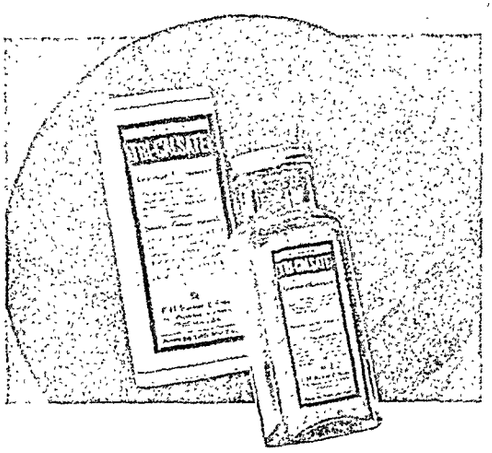
Creamalin has now been used in thousands of cases of gastro-duodenal ulcer with gratifying results. Many of the cases treated were resistant to therapies based on combating the acid factor by chemo-neutralization. The special technique employed in preparing Creamalin yields a product of unusual antacid action — *one volume combining with fourteen volumes of N/10 HCl in one hour by physical fixation.*

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pentathal and is to be supplied by Abbott in July.

SPINAL ANESTHESIA. *Sise* advises the use of pontocaine with 10% glucose in 4 to 4½ c.c. amounts as a rapid, accurate and safe method of spinal anesthesia.

Stein and *Tovell* report their observations regarding the indications, contra-indications and technique of spinal anesthesia and report the incidence of headaches occurring postoperatively.

Anderson reports an unfortunate case of trophoneurotic gangrene of the extremity following spinal anesthesia. States 18 such cases have been reported since 1906.

OIL ANESTHESIA. (Also see Fissure and Pruritus). *Morgan* cites the results of 100 cases where satisfactory anesthesia was obtained in anal surgery in the use of almond oil containing 1.5% procaine hydrochloride, 6% butyl-para-aminobenzoate and 5% benzyl alcohol. Uses 20-30 c.c. and obtains anesthesia 7-28 days and relaxation 5-16 days.

OTHER DRUGS. *F. C. Smith* reports on the use of diothane in 73 cases where the anesthetic was used in at least 5 c.c. amounts for office excision work and combined with general anesthesia to allay postoperative pain.

Nathanson and *Daland* studied the effects of dilaudid in 115 cases and report it acts twice as rapidly as other narcotics, had little hypnotic effect, and but little effect on the gastro-intestinal tract. It, however, causes respiratory depression. Rectal suppository action was better than the usual opiates, being more rapid and prolonged given with aspirin, oral effect was better than aspirin and codeine.

Anderson, E. L.: A Case of Trophoneurotic Gangrene of the Extremity Following Spinal Anesthesia. *J. Lancet*, 55:800, 1935.
Lundy, J. S.: High Caudal Block Anesthesia. Surg. Clin. North America, 15:1271, Oct., 1935.
Lundy, J. S.: Intravenous Anesthesia: Preliminary Report of the Use of Two New Thiobarbiturates. *Proc. Staff Meet., Mayo Clin.*, 10:536, Aug. 21, 1935.
Lundy, J. S.: Clinical Use of Anesthetic Agents and Methods. *J. A. M. A.*, 104:2313, June 29, 1935.
Morgan, C. N.: Oil-Soluble Anesthetics in Rectal Surgery. *Brit. M. J.*, 2:938, Nov. 16, 1935.
Nathanson, I. T., and Daland, E. M.: Use of Dilaudid in Treating Patients with Cancer. *New England J. Med.*, 213:741, Oct. 17, 1935.
Sise, L. F.: Pantocain-Glucose Solution for Spinal Anesthesia. Surg. Clin. North America, 15:1501, 1935.
Smith, F. C.: Use of Diothane as Local Anesthetic in Proctology. *M. Rec.*, 141:581, June 19, 1935.
Stein, J. J., and Tovell, R. M.: Spinal Anesthesia. *Am. J. Surg.*, 30:282, Nov., 1935.

ANUS AND RECTUM

GENERAL. There are a number of papers that are written on this subject and cannot be included under any separate heading. For the most part they are written for the information of the general practitioner.

Of outstanding importance is that of *Buie's* who emphasizes the necessity of differentiating functional from pathological constipation, determining the source of bleeding and distinguishing types of rectal pain.

Mechling gives a very careful review of anorectal lesions, touching upon the anatomy, embryology, and correlating that with the pathological. Campbell and Fischer write papers excellent from this viewpoint.

Buie, L. A.: Basic Facts Concerning Rectal Complaints in General and Hemorrhoids in Particular. S. Clin. North America, 15:1183, Oct., 1935.
Mechling, C. C.: Interpretation of Anorectal Complaint. *Internat. J. Med. and Surg.*, 48:203, May-June, 1935.

BLEEDING. *E. A. Daniels* discusses rectal hemorrhage and advocates the use of 5% phenol in almond oil as an injection medium therapeutically as well as diagnostically.

Weitkamp distinguishes the different types of blood passed rectally as a determining diagnostic aid. Thus anorectal pathology usually shows bright red blood, blood mixed with pus or mucus signifies the various dysenteries, malignancies, stricture, lymphogranuloma inguinale, polyposis, trauma, and in some cases diverticulitis, and dark or tarry blood high gastro-intestinal pathology.

Daniels, E. A.: Rectal Hemorrhage. *Canad. M. A. J.*, 33:287, Sept., 1935.

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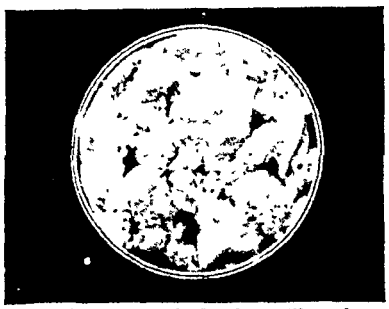


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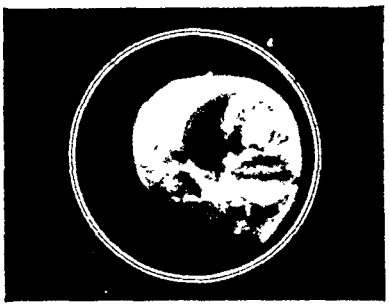
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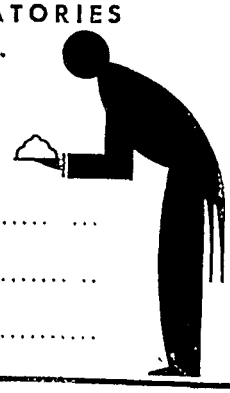
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Weitkamp, A. H.: Bleeding from Anus—Its Significance. *Calif. and West. Med.*, 43:150, Aug., 1935.

CRYPTITIS — PAPILLITIS — PECTENOSIS. *Hirschman* gives a great impetus to proctology by an excellent contribution on the anal crypt as a focus of infection. The paper is masterful and complete. He emphasizes the necessity of crypt investigation and eradication as well as in some cases culture for vaccine therapy. A description is given in detail of the technique of culture and complement fixation, testing the organism itself for antigen or toxin producing properties. The response of the patients to the use of vaccines, etc., fall into three classes.

1. The largest group requiring surgical removal of crypts, sinuses and abscesses, and a more or less prolonged period of vaccine.

2. A class which responds to vaccine therapy in bowel functions.

3. The class of recent origin with complete response to excision. The author emphasizes the need for examination and states the necessity for recognition of cryptitis.

Hinckle discusses the crypt in relation to the pecten band and anorectal infection of various types. States that ruptured crypt in his experience is rarely the cause of a fissure-in-ano, but that infection starts the fibrotic change resulting in pectenosis and later fissure.

Bonnewitz (See Fissure-in-ano).

Papillitis and Cryptitis is reviewed by *H. Z. Hibshman* in the Cyclopedia of Medicine.

Bonnewitz, O. R.: Fissure-in-ano with Complications and Treatment. *J. Am. Inst. Homeop.*, 28:538, Sept., 1935.
Hibshman, H. Z.: Papillitis and Cryptitis. The Cyclopedia of Medicine.
Hinckle, W. A.: The Pecten and Anorectal Pathology. *Clin. Med. and Surg.*, 42:240, May, 1935.
Hirschman, L. J.: Perianal Suppuration as a Focus of Infection. *J. Michigan State M. Soc.*, 34:662, Nov., 1935.

FISSURE

PATHOGENESIS. *Hinkle* describes pectenosis and believes fissure developes in this fibrous band rather than from cryptic origin.

Bonewitz classifies fissures as belonging to the first, second, or third degree stage, the latter characterized by excessive fibrosis or pectenosis. Schoffield in discussing this paper emphasized that the third type was the ulcer stage and that the term pectenosis was somewhat confusing and that more frequently a cryptitis or papillitis are found on examination to be accompanying pathology in the fissure.

Blond states that a fissure is due to necrosis of an inflamed anal varicosity.

TREATMENT. *Hullsiek* in the uncomplicated fissure advocates 1-2 c.c. of 5% quinine urea hydrochloride or nupercaine in oil in 1-3 c.c. In the surgical case advocates partial external sphincter severance and the usual racket shaped wound externally.

Robb advises percain, benzyl alcohol in olive oil as an injection for simple fissure and pruritus.

Sicard describes a method of treating fissure by alcohol injection but claims no cure.

Steinberg reports a modified Gabriel sclution used with excellent results in treating 30 cases of fissure-in-ano, consisting of a nupercaine base of ½ per cent, benzyl alcohol 10%, phenol 1% in 5 c.c. of sterilized oil of sweet almond.

Silbermann reports the use of A.B.A. modified benacol solution since 1929 for anal fissure except in its ulcerated stage where surgery is then necessary.

THE BOWEL



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Since the intestinal canal is a common source of systemic infection, any means of safely and effectively reducing fecal toxicity becomes a logical procedure in a host of conditions.

Morris and Dorst, Burger and other investigators have demonstrated the fact that toxic absorption from the enteric tract may be decreased by the oral administration of sodium ricinoleate—Soricin.

When given in adequate dosage over a reasonable period of time, Soricin brings relief in the treatment of mucous colitis, ulcerative colitis, spastic colitis and a wide variety of other conditions traceable to fecal toxicity, such as vertigo, anorexia, migraine, urticaria, allergic diarrhea, etc.

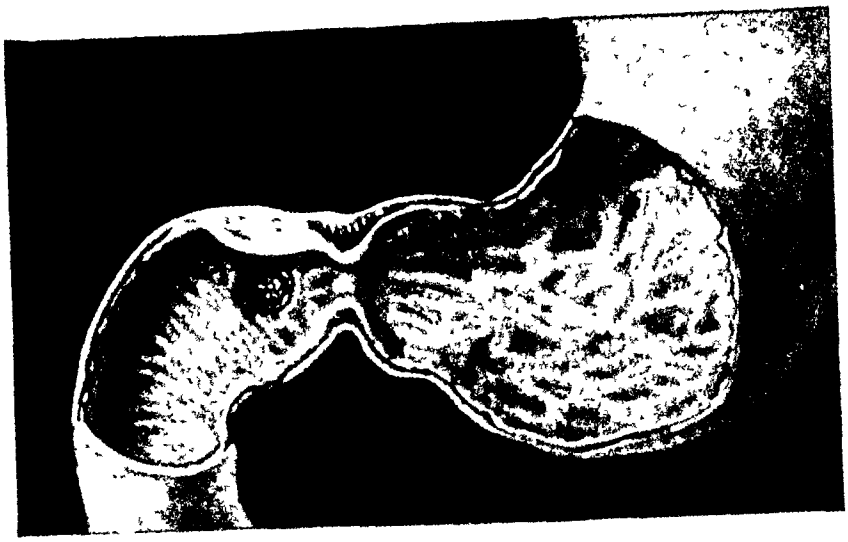
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The Sippy treatment, in its various modifications, is so restrictive as to be irksome to many ulcer patients. They find life a sorry burden.

With the Larostidin treatment there is a minimum of restriction. The diet is rapidly increased to normal, there is no interference with the patient's business or social duties, and there is a remarkable uplift of the spirit that has been smothered by the chronic infirmity.

It has been demonstrated*, moreover, that 70% of the diet-alkali failures make a favorable response to Larostidin. It would seem advisable to start ulcer patients on Larostidin right away.

**Journal A.M.A.*, April 25, 1936, page 1457

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Fissure is reviewed by *H. E. Hibshman* in the Cyclopedia of Medicine.

Blond, K.: (Spontaneous Thrombosis of the Inferior Hemorrhoidal Plexus). *Med. Klin.*, 2:880, July 5, 1935.
Bonnewitz, O. R.: Fissure-in-ano with Complications and Treatment. *J. Am. Inst. Homeop.*, 28:538, Sept., 1935.
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Hullsick, H. E.: Diagnosis and Treatment of Anal Fissure. *J. Lancet*, 55:369, June 15, 1935.
Robb, D.: Injection Treatment in Surgery, with Special Reference to Anorectal Region. *New Zealand M. J.*, 34:319, Oct., 1935.
Sicard, A.: (Alcoholization in the Treatment of Anal Fissure). *Presse Med.*, 43:1227, July 31, 1935.
Silbermann, M.: Anal Fissure and Its Non-operative Treatment. *Virginia M. Monthly*, 62:376, Oct., 1935.
Steinberg, N.: Recent Advances in Treatment of Rectal Diseases by Injection Methods in Ambulatory Patients. I. Use of Gabriel's Modified Solution in Treatment of Fissure-in-ano. *New England J. Med.*, 213:162, July 25, 1935.

FISTULA

ANORECTAL FISTULAE. *McKenney* reviews "Fistulas in the Anorectal Region, and Perianal and Perirectal Abscesses" in all their phases in the Cyclopedia of Medicine.

Kaufmann recommends ambulatory fistulectomy and advises destroying the absorptive surface of the mucosa, use of the seton and attempts to produce an exteriorized flat normal cicatrized wound.

Läwen describes his fistulectomy as one where the sphincters are left intact and the fistulous cavity after complete tract excision obliterated by placing silk sutures into the outer rectal ampulla and through the external wall of the cavity.

Cabanie describes his technic for fistulectomy that seems no different than many ordinarily have done. The cardinal points are complete dissection, sphincter severance, mucosal suture, sphincter suture and an open ischiorectal wound. He removes an anal drain on the 5th day.

Gordon-Watson and *Dodd* explain the course of many fistulas and abscesses by reason of perianal intramuscular glands present deep to the internal sphincter which are for the most part vestigial remains of a more highly developed prenatal duct and gland. They explain the cause of many a deep seated pelvirectal abscess and fistula on this basis and state their removal is necessary for cure to be effected.

W. J. Martin, Jr., in an excellent paper on fistula-in-ano states the cure should be over 95%. Failures are commonly due to excision or incision of the tract with suture of the internal opening or failure of internal opening excision because not found. The paper details many practical aids for the general practitioner.

Prioleau cautions against early sphincter division where the sphincter ani is extensively involved.

Wintsch advises that two stage operations in the treatment of the complex fistula may be necessary but when careful dissection is done on stage suffices. Several cases are given in detail.

INTESTINAL FISTULAE. A traumatic rectojejunal fistula is reported by *Caeiro*. It resulted from a fall on a wire fence with perforation through the anus.

Leland cites a simple vesical calculus resulting in transverse colon fistula.

Raiboff reports a renocolic fistula.

Ranson and *Coller* record 94 cases of external intestinal fistulae other than artificial anus, rectovaginal, and enterovesical fistulae. 13 were tuberculous, one was actinomycosis, 30 were associated with appendicitis, 7 cases of which were cecal or sigmoid, and 10 were undeterminable origin.

Saleh reports a rare case of duodenocolic fistula from carcinoma of the hepatic flexure.

Scott reports 6 cases of rectal trauma, one of which resulted in rectourethral fistula. The repairs were all made at the time of injury excepting



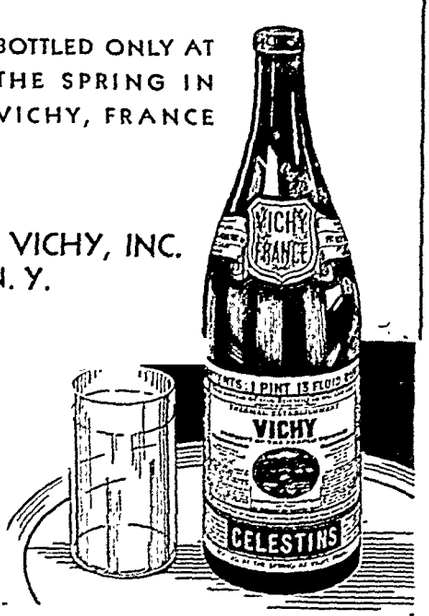
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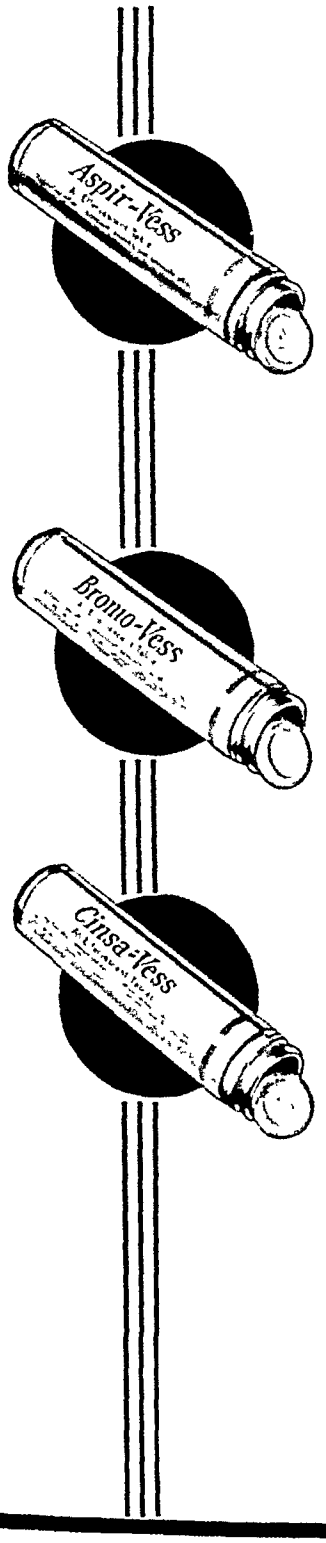


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The final solution is definitely alkaline, which combats the associated acidotic condition usually encountered, and likewise increases tolerance.

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the rectourethral fistula. This was treated by injection with Carnoy's solution and by fulguration of the urethral fistulous stoma. All cases treated carefully post-operatively, no bowel movements being allowed for 12 to 16 days.

Cabanie, G.: (Treatment of Anal Fistulas by Complete Excision and Partial Suture). *Paris Med.*, 1:587, June 22, 1935.
Cabanie, C.: (Partial Suture Following Excision of an Anal Fistula: Operative Technique). *Rev. de Chir.*, 54:633, 1935.
Gordon-Watson, C., and Docc, H.: Observations on Fistula-in-ano in Relation to Perianal Intramuscular Glands, with Reports on Three Cases. *Brit. J. Surg.*, 22:703, April, 1935.
Läwen, A.: (Surgical Treatment of Incomplete Fistulas of Ischiorectal Fossa). *Zentralbl. f. Chir.*, 62:1746, July 27, 1935.
Leland, H. L.: Vesico-intestinal Fistula. *New England J. M.*, 213-44, July 11, 1935.
McKenney, D. C.: Fistulas in the Anorectal Region, and Perianal and Perirectal Abscesses, The Cyclopedia of Medicine, p. 1074, 1935.
Martin, W. J., Jr.: Etiology and Surgical Treatment of Anal Fistula. *Kentucky M. J.*, 33:287, June, 1935.
Prioleau, W. H.: Ischiorectal Abscess and Rectal Fistula. *J. South Carolina M. A.*, 31:167, Sept., 1935.
Raiboff, P. J.: Acquired Renocolic Fistula. *Ann. Surg.*, 101:1291, May, 1935.
Saleh, A. H.: Duodenocolic Fistula. *Lancet*, a:1117, Nov. 16, 1935.
Scott, W. W.: Repair of Rectal Tare and Rectourethral Fistula: Report of Six Cases. *J. Urol.*, 33:643, June, 1935.
Wintsch, C. H.: Treatment of Complex Rectal Fistulae. *J. Am. Inst. Homeop.*, 28:537, Sept., 1935.

FOREIGN BODY. *Kraker* reports a foreign body in the rectum and sigmoid consisting of a half pint whiskey bottle 6½ inches by 3 inches by 1½ inches with a curtain cord and galvanized wire 3/16 inch in diameter attached to the bottle neck. Posterior proctotomy was done necessitated because of wedging against the ischial spines.

Manizade reports a foreign body which resembled a malignancy by reason of the accompanying local inflammation.

Wakeley and *Willway* in one of 11 cases reported where intestinal obstruction occurred by gall stones state that a large gall stone lodged in the rectum and necessitated digital removal.

Wyker reports a foreign body consisting of a cold cream jar 3 inches long, situated 3½ inches within the rectum. Laparotomy and sigmoid incision was done to remove it.

Kraker, C. A.: Foreign Body in Rectum and Sigmoid. *Am. J. Surg.*, 29:449, Sept., 1935.
Manizade, M. C.: (Clinical Aspects and Differential Diagnosis of Inflammatory Foreign Body Tumors Formed Around Chicken Bone in Sigmoid). *Wien. Klin. Wchnschr.*, 48:1111, Sept. 6, 1935.
Wakeley, C. P. G., and Willway, F. W.: Intestinal Obstruction by Gall Stones. *Brit. J. Surg.*, 23:377, Oct., 1935.
Wyker, A. W.: Foreign Body in Rectum. *Am. J. Surg.*, 29:451, Sept., 1935.

HEMORRHOIDS

WHITEHEAD OPORATION. *Szekely* advises the whitehead operation in certain cases and discusses same.

Calinich reviews 9 whitehead cases operated upon during the past 4 years and finds continence not perfect in some and yet concludes that this operation should be done in severe cases.

INJECTION TREATMENT. *Alley* states that injection with quinine urea hydrochloride is the method of choice but advises against its use during the acute or subacute inflammatory stage. States that only 10% of his cases have the transitory pain or discomfort following its use.

Cardoner discusses non-operative treatment of hemorrhoids.

Vogel describes a syringe for injection treatment with the plunger notched interlocking with a control spring to permit gauging the dose with pharmacologic exactitude to the twentieth of a c.c.

Chène and *Dubarry* advocate the use of 5% quinine urea hydrochloride as injection media and advise this treatment in uncomplicated cases in the vast majority of cases of hemorrhoids treated.

Quigley describes an anoscope with a terminal light for direct visuallization and a slot to admit a 12 cm.-22 gauge needle to permit injection of hemorrhoids under air inflation. The author

REINFORCING THE DIET
of the
CONVALESCENT ULCER PATIENT

The frequency of symptoms of undernutrition in convalescent ulcer patients has prompted several recent studies of the ulcer diet in an attempt to find some means of reinforcing it.

The conclusions drawn from these studies are that (1) while the bland and comparatively fibre-free character of the ulcer diet must be maintained, (2) greater emphasis must be placed on the inclusion in the diet of foods that are rich in their content of minerals and water soluble vitamins.

These conclusions stress the value of Gerber strained vegetables in the ulcer diet. They are uniformly smooth products with a maximum of roughage removed. They are unseasoned. And they are prepared with air excluded, so that the valuable vitamins and minerals are conserved.

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prescribe KARO

ACIDS galore are normally formed in the body and eliminated—carbonic, lactic, phosphoric and sulphuric. They are almost completely neutralized by base from cells, intercellular fluids and blood plasma. The body fluids thus maintain the normal faint alkalinity of pH 7.4.

But the defensive mechanisms of the body capable of preventing changes in reaction may be deranged in disease with consequent acidosis or alkalosis. Acidosis is associated with hyperpnea, diarrhea, dehydration, anoxemia, circulatory or renal insufficiency; alkalosis with excessive breathing, vomiting

Treatment of acidosis is designed primarily to correct the underlying cause. In most types, fluids and fruit juices with Karo are forced every hour. In cases associated with ketosis (except where it is a disturbance in carbohydrate metabolism, as in diabetes mellitus) 20% dextrose is given intravenously at repeated intervals. In case of diabetes, insulin is given, by some authorities, simultaneously one unit for each gram of dextrose, until the condition is controlled.

CAUSES OF ACIDOSIS

EXCESSIVE ACID FORMATION

Acid	*Disturbance*
Aceto-acetic B-hydroxybutyric	Starvation Cyclic vomiting Diabetes Ketogenic diet
Lactic	Asphyxia Intestinal intoxication Respiratory failure Shock Burns

DEFECTIVE ELIMINATION

Metabolite	*Disease*
Phosphate	Nephritis
Carbonic acid	Emphysema Respiratory obstruction Myocardial failure Narcosis

CAUSES OF ALKALOSIS

EXCESSIVE LOSS OF ACID

CO_2	Hyperventilation Tetany Cerebral lesions (respiratory center) Hysteria Excessive crying
HCl	Vomiting Pyloric stenosis Intestinal obstruction

EXCESSIVE INTAKE OF ALKALI

$NaHCO_3$	in Pyelitis in Nephritis

From Kugelmass' "Clinical Nutrition in Infancy and Childhood" — (Lippincott)

Treatment of alkalosis depends upon the cause. The most common variety in children is that resulting from prolonged vomiting with loss of acid, salt and body water. No food is given by mouth except fluids with Karo, and saline intravenously. If alkalosis is the result of alkali administration in the presence of nephritis with poor kidney excretion of salts, large amounts of fluids with Karo will favor excess base elimination. Alkalosis from excess alkali administration is alleviated by forcing fluids with Karo.

In both acidosis and alkalosis, Karo is a carbohydrate of choice in the emergency of treatment. Karo consists of dextrins, maltose and dextrose (with a small percentage of sucrose added for flavor), not readily fermentable, rapidly absorbed and effectively utilized.

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claims better exposure and more accurate hemorrhoidal injection at the apices.

DESICCATION METHOD. *G. D. Graham* describes an ambulatory method by desiccating by use of the Oudin coil. Complete local anesthesia is used. The internal hemorrhoids are blanched and the external hemorrhoids are desiccated around their bases to permit intestinal sloughing.

MUCOSAL REDUNDANCY AND HEMORRHOIDS. In another very excellent paper *Daniels* distinguishes between internal hemorrhoids and redundant mucous membrane which he correctly states occurs not only in the hemorrhoidal zone but frequently may rise high into the ampulla. The author by means of a long proctoscope injects high into this area. He also combines ligature operation with injection in correcting internal hemorrhoids.

Riddoch injects internal hemorrhoids in the presence of fissure after anesthetizing it previously.

Chabreyroux gives vaccine treatment locally or vaginally for hemorrhoids.

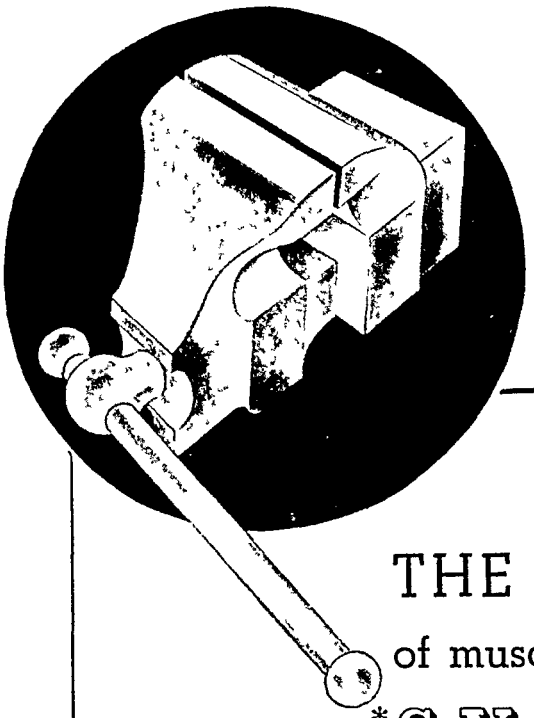
Alley, R. C.: Internal Hemorrhoids: Treatment by Non-surgical Methods. *Kentucky M. J.*, 33:228, May, 1935.
Calinich, G.: (Experiences with Whitehead's Operation for Hemorrhoids). *Zentralbl. f. Chir.*, 62:1154, June 1, 1935.
Cardoner, Planas, A.: (Non-surgical Therapy for Hemorrhoids). *Rev. Med. de Barcelona*, 23:325, April, 1935.
Chabrevroux: (Local Vaccinations in Treatment of Hemorrhoids). *Bruxelles-med.*, 15:916, June 16, 1935.
Chêne, P., and Dubarry, J.: (Hemorrhoids and Sclerosing Treatment). *J. de Med. de Bordeaux*, 112:555, 1935.
Daniels, E. A.: The Hemorrhoidal Lesions: Its Radical Cure by Submucous Injections with or without Ligature Operation. *Am. J. Digest. Dis. and Nutrit.*, 2:631, Dec., 1935.
Graham, G. D.: Desiccation of Hemorrhoids. *Arch. Phys. Therapy*, 16:741, Dec., 1935.
Quigley, T. B.: Injection Treatment of Hemorrhoids. *J. A. M. A.*, 105:1268, 1935.
Riddoch, J. W.: Treatment of Internal Hemorrhoids. *Practioner*, 134:673, May, 1935.
Szelely, L.: (The Whitehead Operation). *Zentralbl. f. Chir.*, p. 1535, June 29, 1935.
Vogel, F.: (Injection Therapy of Hemorrhoids). *Wien. Klin. Wchnschr.*, 48:872, June 28, 1935.

NEUROLOGICAL AND INFECTIOUS ANORECTAL SYNDROMES

Huard presents a very interesting and excellent paper on the various anorectal disorders following or associated with *dysentery*, particularly that of amebiasis. Cutaneous perineal amebiasis he states is probably fairly common but difficult to diagnose. Hemorrhoids, perianal abscess, fistula, stricture and prolapse following dysentery are discussed from a surgical point of view. Cancer may be simulated by, may simulate, or may be associated with the dysentery.

Smiley cites a case of fistula-in-ano associated with sciatica which was *cured by fistulectomy.*

Thaysen reports 3 cases of proctalgia fugax and cites others where a syndrome of periodic transient, spasmodic, and frequently violent anal and rectal pain not accompanied by reflex symptoms or anal spasm occurs. He believes



THE VISE-LIKE GRIP

of muscular spasm is relaxed by

*SYNTROPAN

Morphine often *increases* contractions. Ockerblad and Carlson, for example, found that morphine increased peristalsis in the human ureter. Patients with ureteral colic had renewed spasms of pain—worse than before—after morphine. (*South. Med. Jour.*, 29:2, 166).

Syntropan does not depress the pain centers in the cortex. It acts at the seat of the trouble; it overcomes the spasm, provides real relaxation.

Prescribe Syntropan in all spastic conditions, such as gastro-spasm, nocturnal enterospasm, vesical and urethral spasm, dysmenorrhea, spastic colon, and spasms in the respiratory and circulatory systems.

PACKAGES: Oral tablets, in aluminum tubes containing twenty 50-milligram tablets. Ampuls in packages of six 1-cc ampuls, each containing 10 milligrams.

DOSAGE: For oral administration, 1 tablet (50 milligrams) 3 or 4 times a day, or as required. For parenteral administration, ampuls (1 cc = 10 milligrams) 3 times a day, or as required.

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this due to sigmoid spasm and differentiates it from rectal neuralgia as described by Albu, Gant and others.

Carter reports a similar case in a later issue of the same journal.

Carter, H. S.: Erythromelalgia and Proctalgia Fugax. *Lancet*, 2:372, Aug. 17, 1935.
Huard, P., Renucci, N., and Hiep, N. T.: (Anorectal Dysenteric Syndromes (Excluding Rectorrhagia) of Surgical Nature). *Bull. Soc. Méd. Chir. de l'Indochine*, 13:452, May, 1935.
Smiley, K. E.: Sciatica Secondary to Fistula-in-ano. *Calif. and West. Med.*, 43:151, Aug., 1935.
Thaysen, T. E. H.: Proctalgia Fugax: Little Known Form of Pain in Rectum. *Lancet*, 2:243, Aug. 3, 1935.

PROLAPSE

Huet reports a case of fixation of the colon to the broad ligament of the uterus combined with a uterosacral fixation for prolapse.

Mühling describes the injection of 70% alcohol for the correction of anal and rectal prolapse, the protein precipitation, dehydrating and cauterizing effect being responsible for the result gained.

Schmidt describes an original operative method which he terms "gynecologic" inasmuch as similar to perineorrhapy, *a triangular piece of anorectal segment on the* sacral side is excised and the lateral walls are united with deep silk sutures.

F. C. Smith distinguishes between prolapse and procidential according to the Martin classification.

Huet, P.: (Prolapse of Lower Colon in a Patient with Amputation of the Rectum; Operative Treatment). *J. de Chir.*, 46:363, Sept., 1935.
Mühling, A.: (Anal and Rectal Prolapse and Its Treatment. *Muchen. Med. Wchnschr.*, 82:1156, July 19, 1935.
Schmidt, W. T.: (Prolapse of Anus; Surgical Therapy). *Med. Welt*, 9:685, May 11, 1935.
Smith, F. C.: Protrusions from the Anus. *Med. Rec.*, New York, 142:533, 1935.

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Dr. Ely Joins Stearns Staff

Frederick Stearns & Company announce the appointment of Lloyd L. Ely, M.D., as medical director.

The addition of Dr. Ely to the scientific staff of this well known pharmaceutical house is a definite step in the research and professional expansion which Mr. Frederick S. Stearns has been fostering for the past several years.

Dr. Ely is a graduate of the State University of Iowa, and after his interneship acquired some valuable clinical experience with Dr. Frank Smithies, famous Chicago internist and gastroenterologist.

In addition to his private practice in Chicago, Dr. Ely also held teaching appointments at the medical schools of Illinois and Loyola.

Always interested in diabetes and in the development of useful therapeutic agents, Dr. Ely in 1926 joined the Lilly medical staff, where in 1931 he became director of the Department of Medical Therapeutics. His acute interest in diabetes and the recent advances by Frederick Stearns & Company in the development of more promising forms of insulin led him to join the staff of the latter organization.

Dr. Ely has a wide acquaintance with clinical investigators and his association with Frederick Stearns & Company is especially significant at this time, because of the intense research activities being carried on in the Stearns Scientific Laboratories.

Dr. Ely has been a member of the Chicago and Indianapolis Medical Societies, the Illinois and Indiana State Medical Associations, the American Medical Association and the Society for the Study of Internal Secretions.

(Advertisement)

VITAMINS IN CANNED FOODS

V. VITAMIN G

By 1925, it was apparent that the anti-neuritic vitamin B of earlier investigators was in reality a combination of several vitamins. In that year, Goldberger postulated the existence of a second vitamin associated with the so-called vitamin B "complex" which he designated as the P-P or pellagra-preventive factor. Evidence has been offered that this factor—subsequently named vitamin G—exerts a specific action in the cure and prevention of human pellagra and a similar condition in experimental animals (1).

Since Goldberger's pronouncement, considerable research has been devoted to resolution of the vitamin B complex and, what is equally important, to testing the specificity of vitamin G in the cure of human pellagra (2).

The findings in the laboratory and clinic have not, in some respects, been entirely in accord (3).

As reports of further investigations appeared in the literature, it became clear that the vitamin B complex had been aptly named. At one time claims were made for the existence of as many as eight factors in this complex (4).

While later work has reduced this number, we know today that what has been considered in the past as vitamin G is, in reality, a combination of several factors. A relation between experimental cataract and vitamin G has been described and, recently, another associated factor was postulated (5).

The significance of these individual factors in human nutrition has not as yet been established. However, regardless of this fact, students of nutrition are agreed that we must provide for the inclusion of so-called vitamin G—admittedly a complex—in the daily dietary. It is also obvious that until more is known about the individual components of the complex, we must continue to depend upon present day bioassay methods to determine the "vitamin G" potencies of foods.

In this connection, many canned foods have been found by comparative studies to retain their original vitamin G potencies as measured by methods now in common use (6).

Investigators in the U. S. Public Health Service have described their values in the control of human pellagra (7).

Commercially canned foods, therefore, may be used with confidence that they will supply amounts of vitamin G consistent with the amounts present in the raw food materials.

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(1) 1926 U S Pub Health Report, *41*, 297
(2) 1934 Am J Med Sci, *187*, 512
1935 J Am Med Assoc, *104*, 1377
(3) 1932 J Am Med Assoc, *99*, 120
(4) 1933 J Nutrition, *6*, 559
(5) 1934 J Nutrition, *7*, 97
1936 Science, *83*, 17
(6) 1932 J Nutrition, *5*, 307
1932 Ind Eng Chem, *24*, 457
(7) 1932 J Am Med Assoc, *99*, 95

This is the eighteenth in a series of monthly articles, which will summarize, for your convenience, the conclusions about canned foods which authorities in nutritional research have reached. We want to make this series valuable to you, and so we ask your help. Will you tell us on a post card addressed to the American Can Company, New York, N. Y., what phases of canned foods knowledge are of greatest interest to you? Your suggestions will determine the subject matter of future articles.

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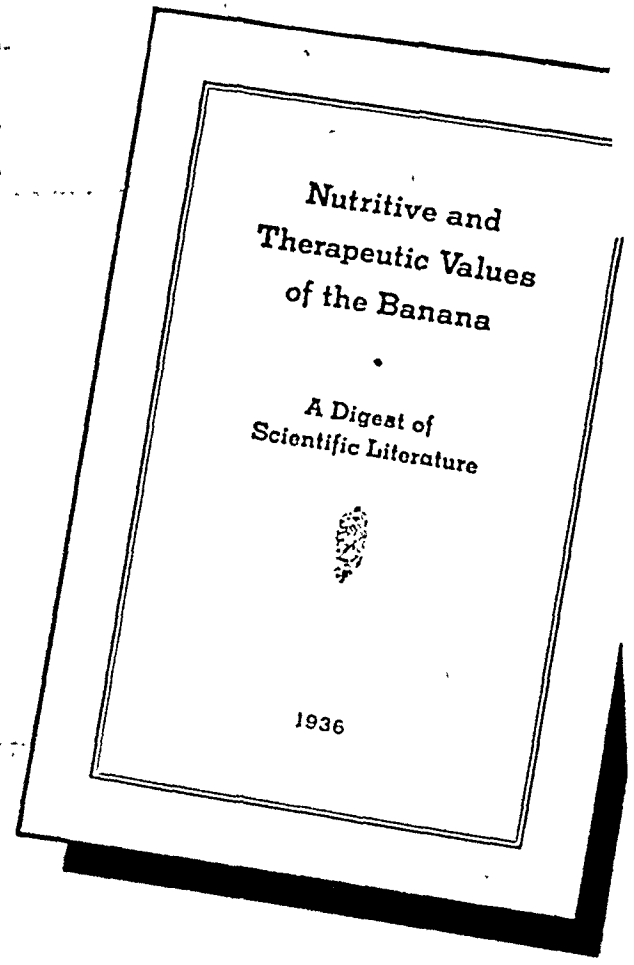
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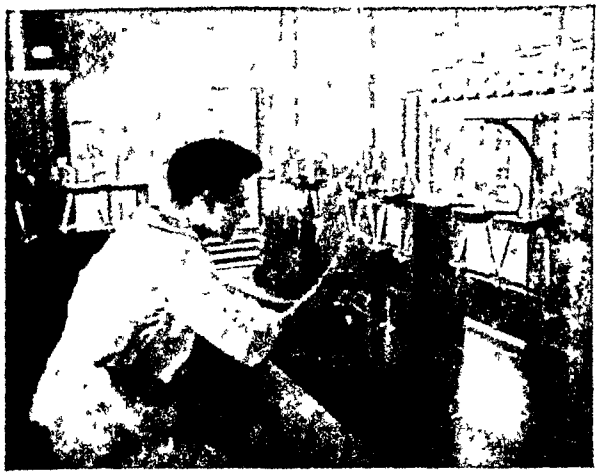
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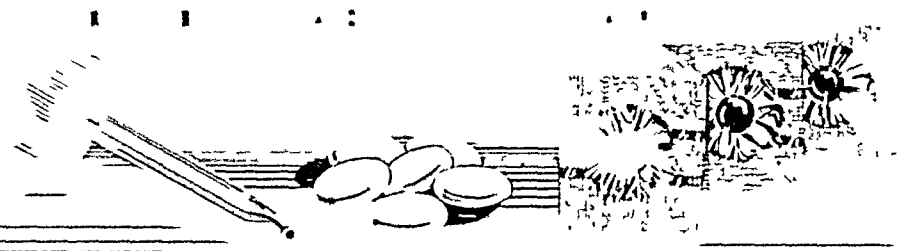
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Growth and Development of the Child, Part III, White House Conference on Child Health and Protection, New York, 1932, p. 213.

BUT— many diets are acid-forming

AS pointed out in the Journal of the American Medical Association (Queries and Minor Notes, 103:701, 1934), "... most high carbohydrate foods of the artificial and refined types are lacking in the basic elements. These basic ions, such as sodium, potassium, and calcium, are necessary for the neutralization and excretion of the various acid waste products of the body. Hence carbohydrates may be implicated in the occurrence of such an acid state by displacing other necessary food products from the dietary."

Ordinary cereals and cereal products, meat, and eggs—all produce an acid ash when burned in the body, yet they form the mainstay of the average diet. Although this preponderance of acid-forming foods is not definitely known to have great significance for the health of normal adults, a number of authorities advocate a basic or alkali-forming diet for children and pregnant women.

INFANCY AND CHILDHOOD. "Alkaline diets are essential for infancy where growth is rapid," declares Shohl. He calculates the need as 10 cc. excess of 0.1 normal base per kilo per day.[1] Babies fed on breast milk stored an excess of base over acid, the range being from 31 to 56 cc. 0.1 N base per day, is the finding of the Committee on Growth and Development of the White House Conference on Child Health.[2] Lippard and Marples observed greater increases in weight of infants receiving basic diets as compared with controls on acid-forming feedings.[3]

PREGNANCY AND LACTATION. Shohl states, "Pregnancy and lactation require additional alkali—a minimum of 150 cc. 0.1 N base per day."[1] Coons and associates, from acid-base balances taken upon normal pregnant women receiving basic diets, determined that the storage of basic substances was even greater than estimated by Shohl. "This may be some indication," they say, "of the magnitude of the maternal needs exclusive of fetus."[4]

As the chief alkali-forming foods are fruits, vegetables, and milk, the ordinary basic diet consisting of these foods is likely to be low in calories and often does not appease hunger. But Pablum—the only base-forming cereal*—offers a way to add muffins, cereal, puddings and similar "filling" foods to the usual basic diet. Pablum, moreover, is richer than ordinary cereals in calcium, phosphorus, iron, and copper and supplies vitamins A, B, and G.

[1-4] *Bibliography on request.* *Mead's Cereal (Pablum in uncooked form) is also base-forming.

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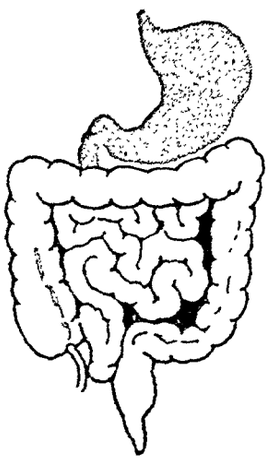
Pablum (Mead's Cereal thoroughly precooked) is a palatable basic cereal consisting of wheatmeal, oatmeal, cornmeal, wheat embryo, alfalfa leaf, beef bone, brewers' yeast, iron salt and sodium chloride.



Cereal	Base	Acid
PABLUM	1.8	
Farina		11.0
Oatmeal		12.9
Wheat, whole		11.5
Cornmeal		5.3
Barley		10.1
Rice		8.1

Figures given in the above table are based on 100 grams of food and represent cubic centimeters of normal acid or base.

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SECTION I—*Clinical Medicine: Diseases of Digestion*

Pyrexia in Gastric Carcinoma*

By

HARRY A. SINGER, M.D.†

and

FREDERICK STEIGMANN, M.D.‡

CHICAGO, ILLINOIS

FEVER as a symptom of carcinoma of the stomach is at present accorded little attention in treatises on gastric malignancy. Although stressed by the earlier writers since Wunderlich (1) in 1856 described the occurrence of pyrexia in malignancy, the modern authors of texts attach very little clinical importance to the presence of fever in carcinoma. Some authors speak of pyrexia in gastric cancer but give the subject merely fleeting consideration (Crohn (2), Smithies (3), Einhorn (4), Riegel (5), Nothnagel (6), etc.), whereas others fail even to mention fever in carcinoma of the stomach (Aaron (7), Cheney (8), Boas (9), etc.). The reasons for relegating the symptom of fever to a position of little or no import are quite apparent. Many writers including a number of authorities on the subject (Kemp 10), Eichhorst (11), Hemmeter (12), Gordon (13) consider fever in gastric carcinoma too uncommon to merit serious consideration from the diagnostic standpoint. Others (Bassler (14), Einhorn (4) take the position that fever, when it does appear, manifests itself too late in the course of illness to be of value to the clinician.

Considering the fact that fever is hardly mentioned by most authors, one is surprised to learn how very common it is when a statistical study is actually made. Fenwick (15) observed pyrexia in one-third of his patients with gastric carcinoma. Freudweiler (16) obtained an incidence of 26% and Friedenwald (17) reported fever in 43% of his series of stomach cancers. Osler (18) makes the statement that fever occurs in from one-half to two-thirds of all cases of carcinoma of the stomach! In the last 1000 cases of gastric malignancy treated at the Cook County Hospital the incidence of pyrexia of substantial degree was found to be 35%. The above statistics should be sufficient to establish the fact that pyrexia is common in cases of neoplasm of the stomach. The current impression that fever appears late is generally but by no means invariably true. As a matter of fact, pyrexia may be the very earliest clinical manifestation of a gastric growth and at times even the only one, the discovery of the tumor being a revelation of the postmortem table. It is this phase of the subject, viz., the occurrence of pyrexia as an initial clinical symptom or sign of carcinoma of the stomach that we wish to discuss and emphasize. Obviously, neoplasms arising in other organs or structures may announce their presence by fever but not nearly so frequently as in gastric growths. Alt and Barker (19) in a follow-up study of 100 cases of fever of unknown origin found that a number died of malignancy and of lymphoblastoma. Kintner and Rowntree (20) made similar observations.

Fever as a symptom of gastric carcinoma is of two types, (1) irregularly intermittent or remittent fever giving rise to the clinical picture of a septicemia of unknown origin (2) more or less regularly intermittent fever associated with chills and sweats, simulating malaria. The greatest number of cases reported in which pyrexia was the initial symptom of a gastric cancer, belong to the septicemic group with only a small number (five) exhibiting the malarial type of paroxysms. The series of cases with the clinical picture of septicemia include the following instances: Archard (21) saw a patient in whom the only symptoms of a malignant growth of the stomach were fever, rheumatic complaints, and edema of the lower extremities. Bassler (14) observed a patient who entered the hospital because of the presence of fever of undetermined origin. In the course of a complete study, a gastric malignancy was found to be the only apparent cause of the pyrexia. Eusterman and Wilbur (22) describe a patient who consulted the Mayo Clinic because of septic temperature, cough, epistaxis and cervical adenopathy. This clinical picture, together with the discovery of ulceration in the mouth, led to the diagnosis of acute septic leukemia. The necropsy, however, disclosed a malignant growth of the stomach which had metastasized to the cervical lymphnodes and brain. Freudweiler (16) reports on two patients who entered the hospital because of fever of obscure origin and who later, while under observation, developed symptoms of malignant disease of the stomach. Kratschmer (23) studied for six weeks a young soldier who presented the picture of a mild sepsis with a soft, systolic apical murmur and a questionably palpable spleen. The correct diagnosis was not made until the patient died, when necropsy disclosed a

*From the Department of Medicine of the Cook County Hospital.
†Late Associate Professor in Medicine, University of Illinois, College of Medicine and Attending Physician, Cook County Hospital.
Dr. Singer died Aug. 21, 1936. His death removes from the ranks of American Gastro-enterologists not only an erudite and charming individual, a great clinician and teacher, but one who gave promise of advancing to the very front rank in his chosen field. *Editor.*
‡Instructor in Medicine, University of Illinois, College of Medicine and Associate Attending Physician, Cook County Hospital.
Submitted August 21, 1936.

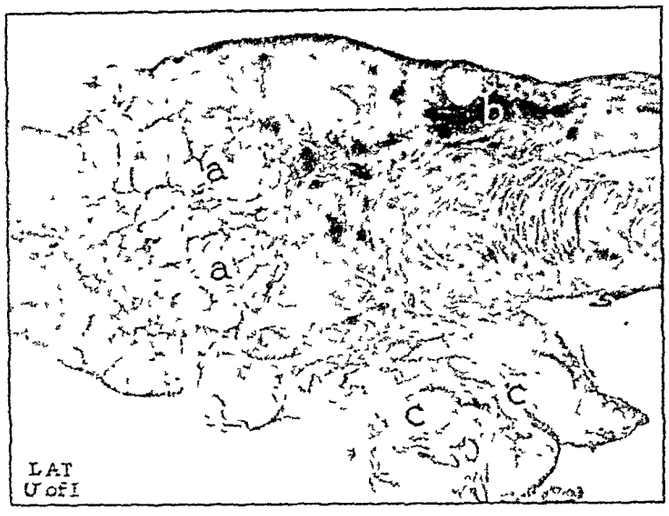


Fig. 1. Small, colloid, carcinoma of the stomach, the first clinical manifestation of which was acute suppurative peritonitis which proved fatal. Almost the entire carcinoma is included in the photomicrograph. The light spaces (a) represent colloid material formed by the malignant cells which are not visible with low power. The dark areas (b) consist of dense accumulations of polymorphonuclear and round cells. Infiltrated omentum (c) is attached to the serosa. No gross evidence of infection of the tumor was detected at autopsy. Magnif. x 4.

carcinoma of the cardia of the stomach with metastases to the pancreas and adrenals.

Of especial interest from the standpoint of fever in the symptomatology of gastric malignancy is Masselot's (24) patient who for twenty-six months before she died suffered periodically from septic manifestations. Various agglutination and other tests failed to uncover the cause of her sepsis. The idea of fever being produced by a silent neoplasm was so foreign that when an X-ray examination disclosed a defect of the pylorus, a gastric neoplasm was not seriously considered. Later, however, when symptoms of gastric disease became obtrusive a laparotomy was performed and an inoperable tumor of the pylorus found. In this case mild gastric symptoms did not appear until a few months before the exitus. Portis (25) presented a male patient of forty-six years, who entered the hospital because of chills, fever, loss of weight and pain in the lumbar region in whom a gastric neoplasm with osteolytic metastases to the spine were found. Septicemia resembling that of typhoid fever was the main symptom in Rhea's (26) patient with carcinoma of the stomach, while in Singer and Shabat's (27) case the abdominal complaints were almost completely overshadowed by manifestations referable to a metastatic suppurative arthritis of the lower spine. Sepsis associated with alternating constipation and diarrhea was the only manifestation of a gastric carcinoma which had perforated into the transverse colon in a patient observed by Starkey-Smith (28). In our present series of four cases reported in detail below the fever which initiated the symptomatology was septicemic in three.

In spite of the fact that malarial-like paroxysms are described in connection with malignancy of the stomach by nearly all authors who discuss at length the subject of fever in gastric carcinoma very few illustrative cases have been described. Hampeln (29) in 1888 recorded in two patients recurrent attacks of chills, fever and sweats which persisted for several months, while gastric complaints appeared only several weeks before death. In each patient a malignant growth of the stomach was found at autopsy. Two other instances are reported by Rovsing (30). One of the patients had malarial-like paroxysms for nearly four years, before a carcinoma of the pylorus was discovered during the course of a complete examination. Resection of the tumor led to full recovery. The other patient manifested chills, fever and sweats for four and one-half months before gastric symptoms appeared. The latter led to the diagnosis of carcinoma of the stomach and subsequent resection with restoration of health. A fifth case reported by Singer and Shabat (27) was that of an ex-sailor who because of chills, fever and sweats was thought to be suffering from malaria. The autopsy disclosed a suppurative arthritis of the lumbar spine with bilateral psoas abscesses. An ulcerating, medullary carcinoma of the stomach located in a silent area (greater curvature, mid-portion) was the only primary site of infection found to account for the purulent arthritis. In only one of the four patients in the present series in whom fever was the first clinical manifestation of gastric malignancy was the pyrexia associated with chills and fever of the malarial type.

The first two patients in the foregoing series will be reported in detail. To conserve space only the bare essentials in connection with cases 3 and 4 will be mentioned.

AUTHORS' CASE REPORTS

Case 1. H. G., a white man of 56, entered the Cook County Hospital, May 29, 1933, because of fever and weakness. According to the history the fever which began several weeks before admission was present daily but did not require the patient to take to bed. Two weeks previous to entrance following the exertion of cranking his car the patient experienced pain in the lumbar region. The backache continued and was present at the time of admission when a substernal pain was also mentioned. There were no other complaints. The patient enjoyed a good appetite, and was free from epigastric pain, nausea and vomiting. At no time was there any digestive disturbance. The remainder of the history was essentially negative.

Physical examination disclosed a well developed and well nourished white male, not acutely ill, but apparently febrile. The temperature by mouth was 102° F., the pulse rate was 110 and the respiratory rate was 28. The systolic blood pressure was 130 mm. and the diastolic 80 mm. The head, neck and lung fields were found to be normal. Soft systolic murmurs were heard at the apex and at the base of the heart. The liver was felt two fingers breadth below the right costal margin. The spleen was not palpated. No epigastric mass was discovered. The back appeared essentially negative except for tenderness on percussion over the lumbo-sacral regions. No other changes of note were present. The Wassermann was negative, the blood chemistry within normal limits, and the urine essentially normal. A roentgenogram of the chest showed a slight infiltration in the base of the right lung.

The patient, feeling quite improved with reference to his back insisted upon leaving the hospital on June 6, 1933, but returned eight days later. During his *second stay in the hospital* the physical signs were essentially the same as those observed at the time of the first admission. The temperature varied generally from 98° to 102° F., but rose occasionally to reach 103° F. The pulse rate was rather rapid. The urine was again reported normal. The hemoglobin was found to be 57%, the erythrocyte count was 3,250,000, the white blood count 9,400 of which 72% were polymorphonuclear leucocytes, 22% lymphocytes, 4% eosinophiles, and 2% monocytes. An electrocardiogram was negative. An X-ray of the spine showed only slight



Fig. 2. An example of infection in another colloid carcinoma of the stomach which ran a febrile course. The deeper layers of the gastric wall are invaded by mucus-producing malignant glands which appear light. In association with the neoplastic elements and extending beyond them are accumulations of cells of an inflammatory nature which stain dark. Magnif. x 33.

osteoarthritic changes in the lumbar region. The Widal test was negative, as was also the agglutination test with *B. melitensis*. A blood culture taken on June 21, 1933, yielded a pure growth of streptococcus viridans. On June 26, the spleen was found to be palpable. In view of the septic temperature, general malaise, palpable spleen and positive blood culture, the diagnosis of subacute bacterial endocarditis was made. The patient again left the Cook County Hospital to enter a private institution.

From the records of the latter it is learned that the patient entered there on June 29, 1933, with similar complaints and practically identical physical and laboratory observations. At this hospital the patient's blood culture yielded again gram positive cocci. The patient was given several blood transfusions in the following four weeks without producing any apparent improvement. He continued to run a septic course and died about five weeks after entrance there with the *ante-mortem diagnosis* of subacute bacterial endocarditis.

The *necropsy* performed a few hours after death disclosed the following significant changes. Along the posterior wall of the distal third of the stomach near the greater curvature was a diffuse, infiltrative lesion. The mucosal surface was a fungating one with many of the areas heaped up into nodular masses. The mucosa was superficially ulcerated, the wall of the involved portion markedly thickened and firm. Many of the nodular areas were seen extending along the mucosal surface of the proximal one-third of the duodenum. Here, however, no ulcerations were present and the nodular areas were more discrete. Along the anterior wall of the stomach, immediately proximal to the fungating growth, the mucosa was thickened. The liver had numerous metastases and weighed 4,375 grams. The spleen was enlarged, weighed 625 grams and had several metastatic nodules. Metastases were found also in the retroperitoneal and mesenteric lymph glands and in the omentum. The heart was essentially normal; its weight being 260 grams. The right upper pulmonary lobe showed a slightly calcified area. The *anatomical diagnosis* was: Adenocarcinoma of the stomach with secondary ulceration; metastatic carcinoma of the lymph nodes, omentum, liver and spleen; old fibrous tuberculosis; cachexia.

Case 2. M. B., a Turkish woman of 51 years of age was admitted to the Cook County Hospital, November 13, 1929, with the following history which was obtained from her son. About one year prior to entrance, the patient noted an irregular fever and weakness. Later in the course of her illness pain in the left side of the upper abdomen appeared. She entered a private hospital where X-rays were taken, but no diagnosis was made prior to her being discharged. No barium meal was administered. Her symptoms continued unabated and the patient grew progressively weaker. Five months prior to admission to the Cook County Hospital the patient developed a severe cough which was productive of a large amount of foul-smelling greenish sputum. This prompted her again to seek medical aid. This time she entered a hospital in connection with a medical school where many tests were performed and many X-rays taken. The patient remained there for six weeks and because of lack of funds was sent to the County Hospital with the diagnosis of undulant fever (positive agglutination in dilutions up to 120) plus lung abscess.

Upon entrance into the Cook County Hospital her complaints were those of vague pains in the left side, fever, weakness, cough and expectoration of a fetid sputum. Her past history was essentially negative except for a "fever" which she had while in Turkey many years prior.

The *physical examination* revealed marked emaciation and pallor. In the left upper quadrant there were tenderness and a sense of resistance as from a mass. An X-ray of the chest was reported as negative. The blood serum gave an agglutination of only 1:80 with *B. abortus* and 1:160 with *B. melitensis*.

The *diagnosis* made by the junior interne, Dr. Melvin Afremow, was pulmonary abscess caused by a malignancy of the stomach with abscess formation and rupture through the diaphragm. The patient grew rapidly worse, and died the third day after entrance before any further studies including X-ray of the stomach could be completed.

The *necropsy* was performed several hours after death by Dr. R. H. Jaffé from whose description the following relevant excerpts were taken. 'The basal portion of the left lung in its medial half is loosely adherent to the diaphragm. Near the anterior aspect of the diaphragmatic surface of the left lower lobe the pleura and diaphragm are defective and a superficial excavation of lung parenchyma is found 5 cm. in diameter and 1 cm. deep, lined by a well-defined membrane 1 mm. in thickness. On the anterior surface of the fundus of the stomach, beginning just below the cardia and extending from the lesser to the greater curvature, is a large mucosal defect nine and one-half cm. in diameter. This mucosal defect leads into a large, supragastric cavity. The wall of this cavity is made up of the liver, and the upper pole of the spleen. The cavity is lined by soft, friable, and firmer cauliflower masses. The sectioned surface of the wall is diffusely white and opaque. The remainder of the gastric mucosa is smooth and covered by blood tinged mucus. The perigastric and peripancreatic lymph nodes are enlarged up to 3 cm. in diameter, firm, smooth and white."

The *complete anatomical diagnosis reads:* "Fungating medullary carcinoma of the anterior wall of the stomach with formation of a large perigastric cavity compressing the liver, extending through the diaphragm and into the left lower pulmonary lobe; metastases to the peripancreatic and perigastric lymph nodes; focal, fibrinous adhesions between the base of the left lower pulmonary lobe and the diaphragm; erosion abscess of the left lower pulmonary lobe; severe brown atrophy of the myocardium,

passive hyperemia and edema of the lungs with compensatory emphysema of the anterior portions; anemia and fatty changes of the liver; fibrosis and slight inflammatory softening of the spleen; anemia and arterio-sclerosis of the kidneys; bloody intestinal and gastric content; senile involution of the internal genitalia; edema of both lower extremities and of the labia majora; advanced emaciation."

Case 3. G. B., a white male of 63, experienced a continuous, low-grade fever unaccompanied by any local symptoms. He had been treated for a grippal infection by his local physician in Gilman, Ill., without any apparent improvement. He consulted Dr. Adolph Kraft of Chicago, who referred the patient to one of us. (H.A.S.). The initial examination in October, 1930, yielded no significant diagnostic information. The patient who had not planned to stay in the city agreed to return to Chicago in a short time for observation and study. He did not return however, until six months later at which time the additional symptom of sharp, knife-like pain felt in the region of the left shoulder, and synchronous with respiration was elicited. No physical signs of pleuritis or other chest pathology were obtained.

On the basis of the history of fever of obscure origin and indications of irritation of the diaphragm probably from the peritoneal side a *diagnosis* of carcinoma of the cardiac portion of the stomach with secondary infection was made. An X-ray of the stomach with the aid of a barium meal disclosed an extensive filling defect involving the proximal end of the stomach.

After a lapse of a few weeks, digestive disturbances consisting of belching, bloating, and epigastric heaviness appeared. The shoulder pain became associated with chest pain which overshadowed the dyspepsia and caused considerable suffering. The fever persisted while loss of weight and strength was becoming quite apparent. The patient grew progressively worse and died at home eight months after the appearance of local symptoms and sixteen months after the onset of fever. No autopsy was performed.

Case 4. F. S., a white male of 54, a gardener by occupation, was in the habit of spending his annual vacation during the winter in the southern part of the country. In 1934, he chose to spend his holidays in Hot Springs, Ark. He felt quite well during his vacation but soon after returning to his home in Oak Park, Ill., early in February, 1935, he experienced chilliness, feverishness and general weakness. He consulted his family physician who diagnosed "flu" and advised him to remain in bed. At the end of two weeks instead of recovering, paroxysms of chills, fever and sweats occurred. The family physician was again summoned and ascribed the illness to malaria and administered quinine. Following ten days of quinine therapy the paroxysms became less frequent and the patient felt somewhat improved. The improvement, however, was only of limited duration, for chills, fever and sweats returned with increased frequency and intensity. Up until June 15, 1934, the patient had had no specific complaint referable to the gastro-intestinal tract except perhaps for lack of appetite. The anorexia had been attributed to the fever. On June 15, however, the patient complained of severe upper abdominal pain which rapidly became diffuse and failed to remit even after medication prescribed by his physician. He developed vomiting, distention and obstipation and his general condition grew progressively worse. On June 17, he appealed to one of his employers, Dr. O. C. Nelson, who felt an epigastric mass and recognized the presence of a diffuse peritonitis. Dr. Nelson advised the patient to enter our service at the University Hospital where the patient died the following day.

The *necropsy* disclosed an ulcerating, necrotizing medullary carcinoma of the stomach with perforation through the infected, necrotic portion of the neoplastic tissue and an acute diffuse fibrinopurulent peritonitis. There was no focus of infection in the body other than the infected gastric malignancy.

COMMENT

The causation of fever in gastric malignancy is at present a matter of conjecture. Some authors consider absorption from the tumor the principal factor in the production of pyrexia. Wassiljeff (31), who reviewed the literature up to 1895, arrived at the conclusion that fever in carcinoma may be due to absorption of tumor cell-production from either breaking down (retrograde metamorphosis) or growth and dissemination. Wassiljeff looked upon the fever as an index of the rapidity of the growth and spread of the carcinoma. Gordon (13) twenty-five years later expressed a similar opinion, viz., that fever was due chiefly to rapid growth and multiplication of carcinoma cells and spoke of "growth fever" as contrasted to "complication fever." Hemmeter (12) who considered fever of rare occurrence in gastric carcinoma believed the pyrexia a consequence of autointoxication. Eichhorst (11) was also of this opinion. Alexander (32) spoke also of carcinoma fever independent of suppurative complications as abscess, etc. Other authors emphasized septic complications due to secondary infection of the carcinoma (Finlayson (33), Muller (34), Crohn (2)). Achard (21) listed a number of local, regional and metastatic infectious lesions originating in gastric carcinomas. A third group of authors did not stress any specific etiology in the causation of fever but mentioned both absorption from the carcinoma or its products and secondary infection (Osler (18), Smithies (3), Freudweiler (16), Bassler (14), Kemp (10)).

Our own investigations lead us to doubt that autointoxication furnishes an explanation for the frequent fever in gastric carcinoma. With regard to absorption due to rapid multiplication and dissemination, it is a daily observation that the extent and rapidity of growth of the neoplasm bears no relationship to the presence or absence of fever. We, among others have observed a considerable number of small carcinomas accompanied by fever where the rate of growth was minimal and the extent of spread negligible. The case of Rovsing (30) cited above in which the tumor was strictly localized and resectible after four years of fever speaks strongly against the occurrence of "growth" fever in gastric malignancy. In connection with absorption from breaking down of malignant tissue, however, it is quite conceivable that pyrexia may develop where rapid and continuous destruction of cells occurs. In the use of radiotherapy for the treatment of hyperplastic and neoplastic growths a brief period of pyrexia is a more or less regular consequence. It is hardly likely, though, that spontaneous retrograde metamorphosis even begins to take on the proportions of artificial destruction and if it does so, that extensive cellular degeneration is as prolonged and persistent as is the fever of gastric malignancy. Furthermore, one observes clinically massive tumors with extensive degenerative changes where fever is completely lacking. One is forced to conclude, therefore, that the autointoxication theory was invoked not because of any scientific or clinical evidence but on account of the failure to identify any demonstrable cause of the fever.

A study of post-mortem material lends support to the belief that the fever in gastric carcinoma is in



Fig 3. An ulcerating carcinoma of the stomach associated with septic manifestations. The invading carcinoma cells which are large and deeply stained are found in association with collections of polymorphonuclear leucocytes which are microscopic abscesses. Macroscopic signs of infection were not apparent to the prosector. Magnif. x 50.

general due to infection. If one observes the character of the neoplasm which is so frequently associated with pyrexia he will notice that it is medullary in type and frequently ulcerated. The gross suppurative lesions which complicate gastric carcinoma are too well known to require more than mere mention. They include infection of the tumor itself, bacterial invasion of the gastric wall (phlegmonous gastritis), perigastric abscess, purulent perigastric lymphadenitis, and distant metastatic, suppurative lesions as in the bones and joints. As pointed out elsewhere (see Singer and Shabat (27)) a purulent bone or joint of obscure etiology in a middle-aged or an elderly individual should lead to an investigation for a silent carcinoma in the gastro-intestinal tract and most especially in the stomach

When gross suppuration is absent a careful microscopic study generally discloses a portal of entry in the stomach for bacteria. The ulceration may be inconspicuous and seen only with the aid of the microscope. That pathogenic organisms enter the systemic circulation through the defective area is attested to by the subjacent zone of inflammatory reaction. In most instances the infiltrated polymorphonuclear leucocytes are more or less intact (Figs. 1, 2). In a few cases, however, liquefaction necrosis occurs and minute intramural abscesses develop (Fig. 3). The occurrence of systemic invasion by bacteria in the absence of gross suppuration has been known for many years. Hanot (35) referred to a septicemic form of gastric carcinoma in which positive blood cultures were at times obtained during life. Fromme (36) explained in 1907 that "due to mechanical damage of the carcinoma, large lymph routes are opened and numerous bacteria are introduced into the lymph glands, the barriers of which become overwhelmed." The microscopic demonstration of ulceration surrounded by an inflammatory zone merely offers further evidence to the assumption that the portal of entry is located in the new-growth.

It was, and still is, generally believed that the presence of fever in gastric carcinoma adds greatly to the gravity of the prognosis. This view was fully justified before gastric resection was more or less universally feasible since the sepsis if unchecked frequently produces death before the carcinoma has exerted much influence upon the patient's general health. However, in this day of advanced surgical development the opinion that fever in the words of Einhorn (4) "is always a bad omen" is hardly tenable. The prognosis is dependent chiefly upon the operability of the neoplastic growth since the successful removal of the tumor as in the two cases of Rovsing (30) eliminates the focus of the sepsis. The bulk of the tumors which ulcerate and permit entrance of bacteria into the tissues and lymphatics and thence into the blood stream are soft, polypoid growths which protrude into the gastric cavity. These intralumenal growths are not infrequently attached to the gastric wall by a relatively narrow pedicle and free from extensive metastases. Hence they lend themselves admirably to complete extirpation. The dense, scirrhous carcinomas, which do not tend to ulcerate and become secondarily infected, exert their growth energies in contrast to the medullary tumors toward extension along the wall of the stomach and into the extragastric structures rather than into the lumen. These scirrhous growths are generally unaccompanied by fever but yet are notoriously unfavorable cases from the standpoint of both resection and recurrence. Fever in carcinoma therefore should not be considered an ominous sign for it may lead to early recognition and timely removal of the growth.

SUMMARY AND CONCLUSIONS

The symptom of fever in gastric carcinoma is accorded but little attention in texts and in medical literature. The reasons generally given are twofold. In the first place, pyrexia is considered to be infrequent in occurrence and secondly its appearance takes place too late in the course of illness to be of value for purposes of diagnosis.

Statistical studies indicate that fever is of quite common occurrence for the incidence of pyrexia in gastric malignancy is approximately 35%. Furthermore, attention to clinical histories shows that in a certain (although very small) percentage of cases, fever constitutes the initial and at times the only clinical manifestation of the growth.

Four cases of gastric carcinoma are presented in each of which the initial clinical symptom was fever and its concomitants. The first case was diagnosed clinically as subacute bacterial endocarditis, the second case as undulent fever and lung abscess, the third as malaria, and the fourth was treated for influenza.

The etiology of the fever in gastric carcinoma is in general secondary infection. Where gross ulceration of the growth and apparent suppuration are lacking, careful search almost invariably discloses microscopic defects of the surface of the growth. About these ulcerative sites evidence of marked inflammatory reaction is seen. The zones of inflammation are at times

purulent indicating that bacteria find entrance through these portals to reach the blood stream. The prognosis in gastric cancer is not necessarily rendered ominous by the presence of fever.

In cases of fever of obscure origin occurring in individuals of carcinoma age, roentgen search for a silent malignancy, particularly of the stomach, is indicated.

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The Prognosis in Regional Ileitis*

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IN the last four years a considerable literature has appeared centering around the subject of inflammatory lesions of the small intestine, particularly the ileum. Undoubtedly the publication of the paper by Crohn, Ginzburg and Oppenheimer (1), in which a clinical and pathological description, as well as a name, was given to the disease, helped to focus medical attention on the susceptibility of this segment of the intestine to inflammatory lesions.

The predilection of the terminal ileum as a focus of granulomatous inflammation was pointed out, and the significance of both external abdominal wall fistulae and internal visceral fistulae was emphasized. In this earlier paper based upon 14 examples of the disease, the low-grade chronic course and benign outlook were predominant; occasional cases with the late feature of small intestinal obstruction due to cicatrization were mentioned, those latter representing attempts at spontaneous healing.

In a later paper (2) it was recognized that this very type of benign inflammatory granuloma could involve the jejunum as well as the ileum, a fact which had already been observed by Harris, Bell and Brunn (3), as well as the occasional familial occurrence of the disease in more than one member of a family. Rarely, combined forms of the disease have been noted (4) in which both ileum and colon have been involved. The true interpretation of this type of extensive ulcerating granuloma is still open to interpretation. True ileitis, terminal ileitis, very rarely involves the colon, though in my experience I am willing to recognize such types of complicated involvement.

Dr. A. A. Berg, who has operated upon a large number of cases, takes a different view, holding that all such cases are instances of disseminated ulcerative colitis with extension into the ileum, essentially "right-sided colitis" with incidental overriding of the ileo-cecal valve and a superficial atypical involvement of the mucosa of the terminal ileum. The last word has not yet been said on this subject. Both views may likely be correct. Suffice it to say at this moment that the success of A. A. Berg in extensively resecting these slowly extending types of "right-sided colitis" has demonstrated the fact that the ileum is almost universally involved in that unusual type of disease.

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The experience of other authors on the topic of ileitis as represented in current medical literature has confirmed our first impressions and has amplified and added some interesting features. Bockus and Lee (5), Mixter (6), Colp (7), Clute (8), Brown, Bargen and Weber (9), Cushway (10), Jackman (11), Powers (12), Green and Pompen (13), Erdmann (14), Felsen (15), Golob (16) among others have all described typical and illustrative examples of this recently recognized pathological process. Probstein and Gruenfeld (17) have urged the acute aspect of regional ileitis; Kantor (18), has described its roentgenological appearance, giving it the apt title of the "string sign." At the German Surgical Congress in 1933 the operative experiences of Fischer, Lührmann, Finsterer and von Haberer were extensively discussed (19). In a recent paper read before the American Gastro-enterological Association, A. A. Berg gave his first extensive report on the surgical treatment by resection of 32 cases of regional ileitis.

That the disease is wide-spread and universal would appear from the extensive literature which has appeared in the medical files. Besides the American publications, which geographically cover the United States and Canada, Great Britain, Germany, Holland and Belgium have already contributed typical examples.

Aside from the suggestion of Felsen (15) that bacillary dysentery plays a role, no suggestions as regards etiology have been advanced.

Just this month Koster (20) has added 17 cases of his own, confirmed by operation. He has also discussed in an interesting way the clinical features and the prognosis of 127 cases culled from the literature and posed some interesting queries.

In a disease the course of which covers usually many years, four years of experience and observation is obviously too short a period to allow of safe deductions regarding the ultimate prognosis and the optimal type of treatment. In its most usual form the disease extends slowly over a period of years with low-grade temperature, mild abdominal cramps, moderate diarrhea and with a slowly progressive loss of weight and an advancing anemia.

But several interesting questions suggest themselves. Among these may be mentioned the following:

1. What is the outlook for cases which have undergone radical resection?
2. Is a palliative surgical procedure, such as a short-circuiting operation warrantable, and what is its ultimate prognosis?
3. What is the proper procedure in the acute type of ileitis?
4. What happens to the case of regional ileitis if no operation is performed?

Final answers to these queries are at this time out of the question; more time, more experience and a more diversified study by various internists and surgeons are prerequisites to definite conclusions.

However, my experience with, to date, 68 personally observed cases, justifies the discussion of these various open issues.

1. *Radical Resection:* It is a pleasure to acknowledge the capable surgical cooperation of Dr. A. A. Berg, who not only operated and resected the very first cases observed at our hospital, but whose recent report on the successful excision of 32 cases represents the greatest surgical familiarity and the widest experience known to us at this date. The type of operation advocated by Berg is a wide resection of the diseased process in the ileum, together with the cecum and ascending colon; an anastomosis between the residual ileum and the proximal transverse colon is established. The extent of resection of the ileum is determined (according to Berg) by the degree and latitude of mesenteric lymphyadenopathy, since the enlarged succulent lymph nodes in the mesentery are the surest guides to the extent of the inflammatory process in the ileum.

Thirty-two cases with one surgical death probably represents the optimum result as judged by the experience of a mature and capable surgeon.

The post-operative functional result is good. The shortened alimentary tract predisposes to intestinal movements which are somewhat greater than normal; 2 to 3 daily defecations are the rule, but cramps and urgency are absent; a great gain of strength and weight and hemoglobin is universal. Recurrences are not reported by this author.

Where long segments of the small intestine are removed, frequent defecations of normal intestinal formation may take place, though these are not associated with recurrences of ileitis. In the course of a few months the stools slowly solidify and form, approaching the semblance of semi-solid defecations.

Fistula formation as a post-operative complication does not appear. Both small and large intestine, in the presence of benign inflammatory processes, seem to tolerate extensive resections with little shock and a very low mortality rate; this in contrast to the high risk of any operative procedure where malignancy exists.

In competent hands, a clean and wide resection of the diseased segment of the ileum seems to constitute the summation of most desired procedures; the type of anastomosis, whether to ascending, transverse or even sigmoid colon, seems to be comparatively immaterial. The operative risk being overcome, the ultimate prognosis in this type of chronic ileitis is excellent.

Perhaps the risk of operation could be reduced by a two-stage operation, doing the anastomosis at the first, and the resection at the second.

2. *The Acute Type of Ileitis:* Cases with acute onset, with a history of less than 4 months, are not infrequent, though besides the rule. In 7 instances the symptoms varied from 2 weeks to 4 months, often with high temperature, vomiting, diarrhea and occasional collapse. It is interesting to note that in 3 of these 7 cases, obstructive symptoms were already present at the time of the operation, indicating that within a few weeks, the entire gamut of inflammation, exhaustion, diarrhea, fistulae formation and stenosis may be run. Obviously, the prognosis is altered by the severity and the rapidity of the course of the disease. Two of these patients died; one of these cases had occurred in 1928 before the nature of the disease was known, no operation being performed. He developed many fistulae to the abdominal wall, to the colon, to the bladder, and to other segments of the ileum, as well as a localized peritoneal mass, all within eight weeks.

The other fatal case followed an attempt at resection, death taking place one week later as a result of exhaustion. Five cases survived resection in the presence of the acute lesion; all have remained well. Pallia-

tive attempts at drainage, or of appendectomy, or of skillful neglect seem useless.

However, in the very recent paper by Koster (20), he has operated upon six cases of acute ileitis in all of which he dropped the involved ileum back into the abdomen without attempting resection. At the time of his writing he reports that the patients are apparently well; there is no statement of the duration of observation since the time of operation. I know of two other cases of acute ileitis which was dropped back into the abdomen several years ago, and which is apparently doing well. I believe the issue is still open as to whether an acute ileitis can spontaneously resolve.

It is obvious that resection, even in the acute phase of the disease can be successfully accomplished without too much risk. On the other hand, the cautious surgeon may exercise good judgment in not attempting resection at this stage. He may well be guided by the subsequent course of the case since spontaneous resolution may be complete, or it may be partial, or the case may immediately face complications, whereupon a second operation, and now a resection, becomes mandatory.

3. *The Prognosis of Palliative Short-Circuiting Procedure:* Many surgeons have attempted to relieve or cure the disease by anastomosing proximal healthy ileum to healthy colon, thus short-circuiting the lesion and rerouting the intestinal content over normal mucosa. Studying the records of 16 such cases, leads to conflicting reactions. In nine of these sixteen cases the anastomotic hook-up failed to cure the disease or alleviate the symptoms. Eventually, radical resection was forced, in 3 instances with fatal issue. On the surface, it would appear that palliation is not only futile, but in addition increase the risk of subsequent operation.

On the other hand, I have, by courtesy of both Dr. Richard Lewisohn and Dr. Ralph Colp, knowledge of 6 cases of ileo-colostomy for extensive and severe instances of ileitis. These cases have all been operated within the last year or two years; most of them seem to be doing well, that is, gaining in weight and strength with disappearance of local masses and subsidence of the severe diarrhea; occasional mild cramps and diarrhea persist in some of the cases.

It is much too soon to try to evaluate the ultimate benefit of such a procedure. That short-circuiting frequently fails, there is no doubt; the study of previously operated cases is testimony to its inefficiency. That it may also at times suffice to cure must remain an open question for the time.

In the article by Koster (20), there is a discussion of the benefits of short-circuiting operations with a review of the immediate results in 15 of such procedures. These cases were culled from among the 127 cases reported in the literature, not all of which are true ileitis. In 13 of these 15 cases the short-circuiting seemed to alleviate the symptoms, a rather promising outlook. However, no follow-up should ever be attempted from an analysis of cases in the medical literature since the publication of a case does not end its life history; recurrences are still conceivable even after supposedly successful and closed cases of sidetracking. It is plausible that shortcircuiting a severe lesion may for the moment benefit the patient causing the disappearance of inflammatory masses and improving the patient's general health. However, the ultimate prognosis is, to my mind, still in doubt.

The risk of a palliative short-circuiting operation is small, the risk of resection somewhat greater. Of the latter, the end-result is almost assured of satisfaction. But if a short-circuiting anastomosis can relieve symptoms and cause great gain of weight, it must be considered as a possible satisfactory operation and be given due time and due consideration before it will achieve its true evaluation as a therapeutic procedure.

4. *Unoperated Cases—The Ultimate Prognosis?* Seventeen cases of ileitis in which no direct operative interference has been practiced are now under observation. The diagnosis has been satisfactorily established and confirmed by clinical means aided by roentgenography, or as in five cases, by exploratory laparotomy. In these latter instances the lesions was accidentally found in the course of an appendectomy or a cholecystectomy. Either unfamliarity with the lesion, or surgical caution, or apparent good judgment dictated a policy of skillful neglect, and the lesion was left undisturbed. Obviously the first question which is posed is, Can ileitis heal itself? Is spontaneous resolution without stenosis possible? Or, failing a natural cure, what is the life history of the process? What is its rapidity of advance, and when do complications (fistulae, perforations, stenosis) occur? Seventeen cases followed for 1 to 3 years cannot afford satisfactory answers to these interesting queries at this early date.

Three of these seventeen cases went on to a fatal termination as determined by autopsy; all died of peritonitis and exhaustion. Another unoperated case had to be resected after two years because of a rapidly downhill course with fever, diarrhea, mass formation and obstruction.

Four of these cases without operation are seemingly doing well, gaining weight slightly, showing an occasional slight tendency to diarrhea, but no real abdominal distress and no loss of efficiency. Considering how often in the anamnesis of cases of regional ileitis we obtain a description of mild pain and diarrhea dating 10 to 15 years back, it is not surprising to note in these few cases an apparent standstill of the process following exploratory laparotomy. I strongly suspect that these cases will eventually form fistulae, a mass, or become obstructed, though it take years for that eventuality.

And yet, scientific precision and clear thinking require one to maintain the premise that a complete restoration ad integrum is within the possibilities of nature.

Another four of these 17 cases (unoperated) are obviously not improving; the symptoms of mild bouts of diarrhea and cramps continue, associated with fluctuating slight loss or slight gain of weight. Of these cases I feel that the "writing on the wall" is clearly legible. The remaining cases are lost to the present follow-up, but will, I hope, because of their value for study, be recaptured.

The problem of treating ileitis by medical palliation can be hardly more than stated; in the fulfilment of time and of study lie the answers. Premature assumption may lead to erroneous conclusions. This eventuality is well illustrated by a recent experience patient who had been explored but not resected, well for two years, so well that he was conside instance of spontaneous cure. Acciden

chance he was discovered in another institution where he had been operated upon in an emergency for small intestinal obstruction, and a segment of diseased terminal ileum resected.

A non-roughage diet seems to benefit ileitis cases. Pain, distress and diarrhea are all relieved when the patient is put on a strict non-roughage diet with pureed vegetables and fruits.

One of my cases of diffuse ileojejunitis was, because of the wide spread process, considered a poor surgical risk. She has lost all her symptoms and gained 25 pounds of weight in a few months, the only form of therapy being the insistence upon the elimination of roughage from her diet. Other cases have similarly shown definite clinical improvement on this form of therapy.

There is no medicinal treatment of this disease.

Since obviously two years of complete normalcy of symptoms can simulate good health, then much more time must elapse before final conclusions can be drawn. Perhaps it will be as with ulcerative colitis: who can say when a case is cured, and who insure against a possible recurrence, no matter how long the freedom from symptoms, except where radical resection has been performed?

5. *Fatal Cases:* In a disease as apparently as benign as regional ileitis, it would be interesting to analyze the deaths that occurred in our experience or are known to have happened in cases whose course has been followed. I know of eight such deaths, three of which occurred without the aid of surgery; five deaths followed attempts at surgical procedures, usually with resections. In the three unoperated cases, death resulted from diffuse or localized forms of peritonitis, the formation of an extensive suppurative mass, or as terminal inanition and exhaustion usual with the formation of multiple fistulae. It is fair to say that had these cases been recognized in time, operation would have had a fair chance of success. Careful watchfulness in the face of a spreading and exhausting process availed not at all.

The post-operative deaths also yield interesting data. One case was resected by a general practitioner who should better have known his own limitations. One was an extensive resection of all of the ileum and much of the jejunum; the case had passed as one of non-tropical sprue for some time; the risk of operation was realized at the moment. Two of the remaining cases were complicated by previous anastomoses and short-circuiting operations. In the eighth case death resulted from post-operative exhaustion complicated by the development of a psychosis of a violent nature. In most of these cases, the fatal issue might have been avoided by earlier operation when the unfavorable trend of the case should have been recognized, and possibly better by a direct attempt at resection rather than palliative surgical procedures. Breaking down the mortality figures, it will be seen that of 17 cases not operated upon, 3 died (17.6%), while of 51 cases operated, 5 died (9.8%). In spite of the extent of the procedure, the risk seems twice as great when surgical aid is refused to the patient.

CONCLUSIONS

There are two good reasons why conclusions should not be drawn from the incomplete facts presented in this paper. For one, the series of cases is too small; for two, the time elapsed is too short to allow for decisions to be made. The disease is a long drawn-out process, its life history will probably be written by the next generation of clinicians, its eventual operative management by future surgeons. In the best of hands the prognosis is excellent when a radical resection is performed. The mortality rate is low, the end-result excellent. Palliative short-circuiting procedures, as well as skillful neglect and so-called conservative medical treatment are still on trial, and the prognosis still to be determined.

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On the Possible Relation of Bacillary Dysentery to Non-Specific Ulcerative Colitis*

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SINCE its first description by Wilks and Moxon (1) in 1875 and by Hale-White (2) in 1888, "ulcerative colitis" has been a storm center among gastroenterologists. In his original paper, Hale-White presented these cases, which form the first attempt to establish a group of ulcerative lesions of the intestinal tract with the widest possible varieties of etiology, as a new entity. Of his eleven cases probably only two or three would be considered as even fairly typical today. The lesions found at necropsy varied in distribution from jejunum to anus showing the acutest lesions distally as a rule. This author remarks, "It no more follows that because there is ulceration of the intestine which in some specimens reminds one of dysentery that the disease from which the patient died is dysentery, than because a condition of the larynx quite indistinguishable from diptheretic ulceration is found that therefore the disease causing the ulceration is diphtheria."

In this fashion ulcerative colitis has come down to us through the years, passing through repeated phases of recognition as an entity, followed by renewed attempts to include it in other and more thoroughly established categories. These recurrent episodes have centered almost exclusively about attempts to prove a single inclusive etiology for this condition.

A brief and incomplete enumeration would include as sole causative factors: psychogenic, neurologic, unknown toxic, vitamin deficiency, endocrine deficiency, Bargen diplococcus, streptococcus, amoebic infestation, B. Coli infection, mercury or bismuth poisoning, tuberculous, syphilitic or dysentery infection. In recent years, further attempts have been made to prove the dysentery bacillus to be the only factor involved. In the following an attempt will be made to present the evidence as proposed, evaluate it and discuss the difficulties and sources of error in the interpretation of the data presented.

DIAGNOSTIC CRITERIA

(A) Isolation and identification of B. dysenteriae: From the point of view of scientific accuracy the ideal way to prove the dysenteric origin of a case of ulcerative colitis would be the unequivocal demonstration of the presence of a strain of *B. dysenteriae* in the excreta or in the intestinal lesion of the patient. The culture of these organisms from the stool or ulcerations is fraught with difficulties, not only involving the method of obtaining the type of specimen most likely to yield a positive result but also the more detailed and complex technical procedures involved in choosing media, choosing suggestive colonies, subculture, etc.

There is no doubt that the best results are obtained when the original culture material is removed directly from the bases of the ulcerations with the use of the proctoscope or sigmoidoscope for visualization. This has been repeatedly emphasized by Seligman and Cossman (3), Seligman (4), Egan, *et al* (5), Fletcher and Mackinnon (6), Smyly (7), Hern (8), Mackie and Gaillard (9). Lacking the opportunity to do this, one may still have a reasonable chance for success if cultures of the bloody mucus of a freshly passed stool are made.

Having begun in this fashion, we may then justly enquire as to the possibilities of recovering a specific organism at various stages of the disease. In this connection we may refer to the experience of Martin and Williams (10), who, in repeated cultures taken in a series of 1050 cases occurring in connection with acute epidemic dysentery, were able to recover the specific organism in almost 70% of cases in the first week of illness dwindling to less than 10% by the end of the second week. Similar data are contributed by Seligman and Cossman (3) and Seligman (4). In an especially thorough and important study of chronic dysentery, Fletcher and Mackinnon (6) were able to isolate a specific organism in 88 of 229 patients, (38.6%) who had been affected with dysentery from one to thirteen years previously. Four of these cases had been ill thirteen years before the follow-up examination was made and still presented positive stool cultures. In order to obtain these results we note that 13 of the cases were examined 469 times with positive results on 207 occasions, i.e. about 44% of the cultures were positive. In a somewhat smaller series of cases of known chronic dysentery, varying in duration from three months to five years with an average of one and one-quarter years, Smyly (7) was able to recover specific organisms in 50 of 62 cases, i.e. in 80.6% of his series. Similarly, Thorlakson (11) was able to culture *B. dysenteriae* from the lesions of six of his nine cases (80%). Schürer and Wolff (12) likewise were able to recover these organisms in seven out of nine cases of dysentery over six months in durations. It can be seen that, with the improvement in bacteriological technique in recent years, the incidence of recovery of specific organisms has incresaed remarkably in cases which are known to have been Bacillary Dysentery from the onset.

Having placed the isolated material on Endo plates (or, if desired, on Conradi-Drigalski or Teague medium) these are frequently inspected and the pearly grey colonies isolated to the various sugar media for fermentation reactions as well as glucose agar slants in preparation for specific agglutination reactions. At this point we meet with our first major obstacle. This is due to the marked tendency shown by the various members of the dysentery group to differ from time to time in their fermentative abilities. To no less a degree it is due to the similar variability shown by the members of the B. Coli group so that when first isolated the latter may present fermentation reactions identical with those considered typical of the dysentery group. This has been a matter of daily experience in routine stool cultures so that a uniform policy of repeated subculture has been adopted with resultant elimination of this source of error. Apparently Gardner (15) as well as Lentz and Prigge (16) and Egyedi and Kulka (17) have had similar experience.

Even within the dysentery group itself we find such extreme variability in fermentation reactions that these

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cannot be used as the sole mode of identification of members of this group. Subdivisions of the so-called paradysentery group based on the fermentation of saccharose and maltose are frequently given. Thus we are told that the Park-Hiss type ferments neither maltose nor saccharose while the Flexner variety ferments maltose but not saccharose. The unreliability of such criteria is well shown by the results of Sonné (18), on the influence of the time of incubation on carbohydrate fermentation. He showed that if the fermentation reactions are read in twenty-four hours 42 out of his 74 strains reacted as typically Park-Hiss and the remainder as Flexner, whereas if observed at the end of forty-eight hours the ratios were completely reversed. In addition the fermentation reactions will vary in successive tests at considerable intervals and these fermentation difference may show little correlation with antigenic differences. Such has been the experience of Russon (19), Sonne (18), Kruse (20), Manteuffel (20a), Thomson and Mackie (21), Ledingham (22), Park and Casey (23), Shiga (24), Bauch (25), Gardner (15) and others.

We may then safely conclude that isolation of the bacillus is the only safe method for certain diagnosis of the type of organism causing the infection and that the cultural characteristics have only a very tentative value. The actual nature of the isolated bacillus can only be definitely ascertained by its agglutination by specific sera.

Here again we meet with several sources of error which are in all probability due to variation in the antigenic factors present in the bacilli. For this reason the organisms show a marked difference in their agglutinability with specific sera from strain to strain and from time to time in the strain. Thus we find, for example, an organism which culturally and fermentatively may be considered a member of the dysentery group and yet cannot be agglutinated by specific animal sera. This may be due to one of three factors: 1—Failure to use the specific serum for this variety of organism, 2—Complete or partial temporary inagglutinability, or 3—Actual non-dysenteric nature of the organism which happens to have the cultural and fermentative reactions of the dysentery group. In the first instance, we may remedy matters by using a greater variety of sera so as to include the specific serum for the strain isolated. Real inagglutinability is by no means a rare phenomenon but is usually not permanent and disappears on repeated subculture. These wide variations in sensitivity to specific sera occur both in different races of a single serological group and in the same race at different times. In any case agglutinin absorption methods will almost invariably serve to identify the organism in such instances. The third group has been discussed above and needs no further comment.

(B) The significance of the Agglutination Reaction: As of secondary importance and merely presumptive evidence of the presence of dysentery infection we may mention the agglutination reaction. Here again we have several serious sources of error to contend with. To begin with, positive agglutinations may be obtained with the sera of perfectly healthy individuals where no previous history of dysentery can be obtained. This has caused investigators to establish border line values which however are found to vary from strain to strain and even with a given strain with different authors. Thus the borderline value for B. Flexner has been placed at figures varying from 1/50-1/100 Barrensheen (26) to 1/300 (Egan et al (5)), for B. Shiga 1/20 (Pfuhl (27)), (Jacobwitz (28)) and 1/100 (Egan et al (5)), Schmidt and Umnus (29). This normal agglutinating power has been shown by Burgi (30), not to be attributable to subclinical infections. Healthy sera clump bacilli by virtue of their physico-chemical constitution and independent of any contact with the bacteria in the sense of a previous infection. The intensity of the agglutination varies from species to species and from time to time in the same individual. Above all it varies with the agglutinability of the suspension used for testing the serum. Even in the higher titers one must be extremely cautious in attributing etiologic significance in individual, isolated cases. These positive agglutinations are of diagnostic value only in the presence of significant clinical and cultural support or in cases where definite evidence is presented of contact with a known case of dysentery proven by culture or where the clinical features are very typical.

The difficulty in the interpretation of agglutination reactions is further increased by the frequent occurrence of the phenomenon of cross agglutination. This, to be sure, is more prone to occur with infections caused by *B. Flexner* or the *Hiss-Y* organism but does repeatedly show itself with the other organisms as well and serves to confuse the interpretation of the results. The unreliability of the agglutination reaction is further demonstrated by the occurrence of negative results in cases where the specific organisms may be repeatedly recorded from the stools (Seligman and Cossman (3)). It seems fair therefore to conclude with Flexner that the presence in the blood of agglutinins for dysentery bacilli is of inconclusive value in diagnosis.

(C) Bacteriophagy: Bacteriophagy presents difficulties in interpretation similar to those of the agglutination reaction. From the technical side the use of the plate method to determine lysis is so unsatisfactory and unreliable that results obtained from its use must be dismissed as subject to too great a chance of error. Even with a carefully titrated test tube series of bacteriophage experiments, we usually find so marked a cross lysis with the various dysentery strains that specific interpretation is practically impossible. In addition, we usually find the lytic principle present only during the acute period of the disease as it is beginning to subside so that it is of relatively little value in chronic cases. Furthermore it has been found in "normal," "healthy" individuals further confusing the issue. Thus, Feemster (31) in examining 111 stools none of which were from dysentery patients found bacteriophage present for dysentery organisms in the following proportions: B. Shige, 10 cases; Hiss-Y, 10 cases; B. Flexner, 9 cases; B. Sonne, 6 cases. If one examines the data from thirteen small epidemic outbreaks presented by this author one is struck by the fact that the bacteriophage in itself has no diagnostic value and that even in cases occurring in the course of an epidemic, is of diagnostic value only when a specific organism has been recovered from another case occurring in the same epidemic. These data may be contrasted with those of Winkelstein and Hirschberger (40) who, with a similar but not identical technique, were unable to isolate a bacteriophage from the stools of 45 patients who presented clinical evidence of dysentery.

(D) Incidence and Significance of Chronic Dysentery: The incidence of chronic dysenteric infection has naturally been a matter of great interest and obvi-

ously would have a direct bearing on the problem of the relationship of bacillary dysentery to chronic ulcerative colitis. This of course will depend upon our definition of chronicity and it may be well to take as a border line, an interval of three months from the onset of the original illness. There need not necessarily be continuous clinical manifestations of disease in these cases during the entire period of so called chronicity. However, as can be seen from the above data, recovery of the specific organisms may be successfully accomplished in as high as 80% of these cases, thus indicating their importance as disseminating foci for endemics or epidemics. Using these criteria Froensdorff (43), in a follow up of his war cases of acute bacillary dysentery, was able to find only three chronic cases in a total of 210 (1.43%). Albu (44), on the other hand, on the basis of sigmoidoscopic and clinical observations considers the complete cure and healing of the intestinal mucosa a rare event in bacillary dysentery. Clinically there remains a greater or lesser sensitivity of the colon, which, with a slight stimulus, causes a recurrence of symptoms. In addition he finds sigmoidoscopic changes which persist for years. However, in only two of his cases was he able to recover specific organisms. As a conservative estimate we may take the figures of Leusden (13) who estimated that about 5% of cases of acute bacillary dysentery became chronic. Schurer and Wolff (12) consider that healing of the colon is prevented by the persistence of the original infections. Walko (14), in discussing chronic bacillary dysentery, points out that, in his experience, these cases are practically always infectious, whether merely healthy carriers or chronically ill with persistent or recurrent diarrhea.

(E) Epidemiologic Data: Bacillary dysentery, generally considered a so-called tropical disease with occasional spreads to the temperate zones, is in reality a cosmopolitan disease, endemic practically the year round throughout the entire United States. The data for the State of California have been carefully compiled by Reed (32) for the years 1917 to 1932 and show a wide distribution of the disease through this fifteen year period. An examination of the monthly data on the incidence of dysentery in this country as published in the United States Public Health Reports shows that cases are reported practically each month throughout the year in states from coast to coast. Further investigation of this same source yields the interesting data on the incidence of diarrhea and enteritis for infants under the age of two years as follows:

	Number of cases	*Rate per 100,000*
1931	18,704	15.7
1932	14,375	12.0
1933	15,706	12.5

These data may be compared with the dysentery rate for the same years in adults:

	Rate per 100,000
1931	2.0
1932	1.7
1933	2.2

If, as we feel, we are justified in assuming that the vast majority of the infantile cases were in reality infections with B. Dysenteriae as was shown by Wollstein (33) and Flexner (34), it can be seen how much more frequent are these infections in infancy, at least in these more severe forms, than in adults. This may be contrasted with the relatively infrequent occurrence of chronic ulcerative colitis in the infant age period. Further proof of the endemic nature of these infections is presented by the data presented by Hassler (35) (Leipzig), Silverman (36) (New Orleans), Smyly (7) (Peiping), Smillie (37) (Boston), Thjotta (38) (Norway), Felsen (39) (Jersey City) as well as the data kindly placed at our disposal by Dr. Boldman of the New York City Department of Health which showed the presence of over 500 cases of proven bacillary dysentery in this city during the first ten months of 1935. These occurred in apparently isolated cases as well as in small epidemic outbreaks.

Bacillary dysentery is primarily a human disease widespread throughout the entire world and affecting mankind regardless of age, color, sex, or social status. As indicated above it has a tendency to occur more frequently in infancy and childhood, at least insofar as clinical manifestations are concerned, although no age period is exempt. In our forces overseas, it occurred with almost equal frequency in both the colored and white troops, at times involving practically entire fighting units. On exposure, males and females are equally affected as shown by Hassler (35). In general the disease tends to occur in association with a lack of adequate hygienic facilities and is a disease of filth. Its transmission by food handlers and contaminated water is too well known to require comment. It thus occurs less frequently in the higher social classes where contact infection is less likely to occur.

We thus find ourselves faced with a disease universal in distribution, prone to have a protracted course with a period of potential infectivity commensurate with the duration of the bowel lesions and affecting all age periods, regardless of sex or color but with a tendency to infect infants and young children especially those living in unhygienic surroundings.

COMMENT ON THE RELATIONSHIP OF BACILLARY DYSENTERY TO CHRONIC ULCERATIVE COLITIS

The evidence adduced to prove the etiological relationship between the dysentery group of bacilli and chronic ulcerative colitis consists mainly in the finding of positive blood agglutination reactions for this group of bacilli in cases of chronic ulcerative colitis. Such data have been brought forward by Mackie (9), Thorlakson (11) and Winkelstein and Hirschberger (40). As pointed out above, this by itself cannot be considered as adequate and conclusive proof of the relationship. Bacteriophagy, also employed by these authorities, has similar defects and cannot thus be considered satisfactory, sole evidence of such a direct relationship.

Thus far there have been too few studies carefully performed in accordance with the criteria mentioned above to permit us to evaluate the factor of dysentery infection in chronic ulcerative colitis. Mackie and Gaillard (10) were able to find 18 positive dysentery stool cultures in a series of 83 cases which clinically were considered chronic nonspecific ulcerative colitis. In these 18 positive cultures, there were included 5 strains of organisms which, though presenting typical fermentation reactions, showed no agglutination in the number of specific sera used in the tests. Making the necessary correction in the calculated percentage we find it necessary to reduce this from 22% to 16%. Similar results have been obtained by Winkelstein and Hirschberger (11%) (40). Both of these series consisted of cases which clinically, sigmoidoscopically and roentgenologically were considered to be idiopathic

ulcerative colitis. We may thus draw the conclusion that about 10% to 15% of cases considered clinically to be idiopathic ulcerative colitis rightfully belong to the category of chronic bacillary dysentery. The residual 85% to 90% still remain in the group of the etiologically unknown.

The gross clinical features and course of chronic bacillary dysentery and of non-specific ulcerative colitis resemble each other so closely that differentiation is impossible unless we trace a case to a known and proven epidemic—an unusual event. Similarly the sigmoidoscopic and roentgenologic features are so similar that they cannot serve as reliable methods of differentiation. And finally we find that even on the autopsy table, there are few if any features which serve as adequate criteria for purposes of differential diagnosis.

Despite these close resemblances there are other features which make one suspect that the two conditions are not dependent upon a common etiology. Thus, in contrast to the age distribution of bacillary dysentery as given above, we find a preponderance of cases of non-specific ulcerative colitis in the third and fourth decades with surprisingly few cases in infancy and early childhood. In a series of 392 cases seen in the Mayo Clinic, only 19 occurred between the ages of 2 and 14 years. Another discrepancy is discovered in the sex incidence, in which it is found that the disease occurs about twice as often in women as in men. (Hern (18)). Furthermore, despite the wide spread distribution of epidemic bacillary dysentery throughout the armies on all fronts during the World War, the preponderance of males is at present below the age of forty and mainly in the third decade which did not see service overseas. In addition chronic non-specific ulcerative colitis insofar as it has been reported in the literature is not as prevalent in Central Europe as one would expect from the prevalence of acute epidemic bacillary dysentery during the late war.

Finally, we must contrast the well known lack of infectivity of non-specific ulcerative colitis, for which no authority known to us has ever claimed infective properties, with the equally well known infectivity of cases of chronic bacillary dysentery as pointed out by Walko (14) and Schürer and Wolff (12). Bargen, in the larger series from the Mayo Clinic, was able to find but five instances of familial occurrence while Paulson in the Johns Hopkins Hospital series could uncover only one such instance. It has been our experience that where such cases occur we are much more likely to find a definite etiological agent such as amoebae or dysentery bacilli.

It is our impression that taking the ulcerative colitides as a group there will be found definite etiological agents responsible for a relatively small number and that the larger residual group consists of a heterogeneous conglomeration of conditions with variable etiology. As yet we are aware of no single comprehensive study under controlled conditions as described above, in which any single bacteriological agent has been proved to be the sole etiological factor concerned in the production of this syndrome. Certainly, the data presented as the case for B. Dysenteriae Shiga such a variation in criteria and control study that they as yet cannot be seriously considered as the final solution of the problem.

SUMMARY

We have attempted to summarize and evaluate the data bearing on the relationship of bacillary dysentery to chronic ulcerative colitis. There is presented evidence suggestive of such a relationship which however is not sufficiently complete to be considered more than suggestive. Criteria for the evaluation of relevant data are proposed. The widespread distribution of endemic and epidemic bacillary dysentery is noted—a public health problem of great importance and magnitude. The tendency for acute bacillary dysentery to become chronic is discussed; it points to the necessity of carefully following all acute cases for at least five years in an effort more completely to study the relationship of these diseases to one another.

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Flexible Tube Gastroscopy: Technique*

A Preliminary Report

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THE purpose of this paper is to present as concisely as possible, the technique of flexible tube gastroscopy, and the difficulties that confront a beginner.

THE INSTRUMENT

There are good descriptions of the instrument in the literature, and a detailed description is not necessary in this paper. There are really three of the Schindler gastroscopes in use. These are generally classified by the angle of vision. The original type had a 60 degree angle of vision, and the instrument had the same diameter throughout. The newer, improved, standard type has an 80 degree angle of vision. The rigid metal portion has been made smaller in diameter than the flexible piece, thus giving more comfort to the mouth, and throat, during the examination. It has a better lens system, it is more flexible, and, owing to the wider angle of vision, one may see more of the stomach wall at any one time, an obvious advantage.

Dr. Schindler is now using an instrument with a 50 degree angle of vision; this has greater magnification, and is of some increased value in gastritis. However, it is evident that the 80 degree instrument will remain the standard.

It should be mentioned that it is inadvisable to use house current and rheostat; a dry cell battery with a voltmeter is ideal, and probably necessary. Thus one may be certain of the same *degree of illumination* with each examination. Eight volts are recommended. The voltage, if lower, does not give sufficient illumination, if higher, may damage the light.

There are several *types of tip*. The original instrument was equipped with a straight tip, as described by Schindler in his original paper. Later, on a suggestion from Henning, the gastroscope was made with a bent tip, either solid, or with a rubber finger. There are certain advantages claimed for this. One, that the introduction through the crico-pharyngeal and cardial constrictions is made easier by taking advantage of the curve, also that the advance down the stomach is simplified by using the bent end to separate the folds. The second possible advantage is in the consequent shortening of the tip, enabling one to insert the instrument deeper. It is certain, however, for one not highly skilled in the introduction of instruments into the oesophagus, that the straight tip is easier, safer, and generally more satisfactory.

We have used two main types of straight tip. The first, the one furnished with the instrument, is tipped with a sponge alone. This is a recent development, also a suggestion of Henning. Its purpose is to clean away mucus ahead of the objective. We have come to the conclusion that this is not necessary, and that the sponge is definitely dangerous. It should be used only in certain rare cases when a centimeter or so of added depth is necessary to visualize the pylorus. The sponge definitely drags in the throat and oesophagus. This is easily felt by the operator's hand, and the drag of the sponge on the mucosa may be strong enough to produce slight tears. Severe sore throats frequently followed the use of this tip, and the sponge was frequently found to be covered by blood streaked mucus. None of these things have been noticed since we shifted to the plain, flexible, rubber finger tip.

One type of tip combined the rubber finger with the sponge, but we feel now that the sponge is in no way useful.

It has been suggested that the tip might well be perforated to allow passage over a thread. The flexible rubber finger removes any necessity for this, except possibly where one wishes to look at the stomach in cases where dilation of the esophagus is present, as in cardiospasm.

CHOOSING THE PATIENT

First, in a general way, the beginner had best choose slim, supple patients that are not only cooperative but intelligent enough to allow them to relax. The procedure is usually easier in women than in men. Negroes, in our experience, are almost uniformly difficult. If the beginner selects the proper patients, his difficulties will be much less.

The *indication for gastroscopy*, is any gastric complaint without absolute contraindication.

The *contra indications* are as follows:

1. Any general condition severe enough to render instrumentation or anaesthetization inadvisable, such as asthma, cardiac failure, toxic infection, etc.

2. Any evidence either from the history or findings, that there is encroachment on the lumen of the esophagus, either intrinsically or extrinsically. Intrinsic lesions so encroaching are stricture, benign or malignant.

Extrinsic lesions that may occlude the lumen are: mediastinal tumor, marked dilation of the aortic arch, aneurysm. The latter is particularly feared.

3. Any evidence that there is dilation of the esophagus. One must particularly look for the localized dilation of diverticulum, either pulsion or traction. Patients with esophageal diverticula or cardiospasm, have been gastroscoped (Schindler), but in the former it is hazardous at best and in the latter should be done only with extreme care, or by passing the instrument over a thread.

4. Failure of an Ewald stomach tube to pass smoothly.

5. Any evidence of esophageal varices, or a disease known to produce these, as cirrhosis of the liver.

6. Not a distinct contraindication, but a possible source of danger are the esophagi which end in

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stocking foot deformity. Occasionally the lower end of the esophagus has been seen by X-ray to make a right angle turn before entering the stomach. This angle would tend to be increased by the left lateral position, and although the rubber tip tends to straighten this bend, it seems reasonable to suppose that rough insertion in this type of esophagus, might possibly result in considerable trauma if not in perforation.

The second, third and fourth and possibly the fifth of these contraindications are indications for esophagoscopy.

PRELIMINARY STUDY

Since the gastroscopic examination can be interpreted best in relation to the other findings and is only one part of the examination of the patient, probably all of the other usual methods of arriving at a diagnosis should be done before the actual inspection of the gastric interior. However, the only two necessary preliminary studies are: (a) X-ray of the esophagus, (b) passage of an Ewald stomach tube.

PRELIMINARY TREATMENT

If no obstruction is present, the only preliminary treatment that the patient is given, is one-half grain of luminal three times daily for two or three days, and one-half grain the morning of the procedure. The luminal is given for two purposes: (a) to help relax the patient, (b) to mitigate any cocain reaction.

If obstruction is present, the stomach should be lavaged clean the night before.

For ten or twelve hours before the gastroscopy, the patient receives nothing by mouth except the half grain of luminal with just enough water to swallow the pill. The luminal and water apparently do not produce any appreciable change in the mucosal appearance.

1. The patient is given a preliminary hypodermic injection containing grain 1/6 of morphine and grain 1/150 of atropine. The morphine is not to relieve any pain but to secure relaxation. It has been suggested that by stimulating secretion the morphine may possibly change the mucosal appearance. Dr. Schindler uses only a grain of codeine, and in most cases this should be sufficient. The value of atropine is somewhat dubious. In some cases it apparently increases the spasm at the cardia. Frequently resistance is felt at the cardia when passing the stomach tube after atropinization, when none had been encountered previously. When this occurs, resistance is also met with by the gastroscope.

2. After allowing 45 minutes or an hour to pass, in order to secure the desired action of the medication, the patient is ready for anesthetization of the pharynx.

We began by using the Schindler anesthetization tube with 2% pantocain, containing one drop per c.c. of adrenaline (1-1000). In this method the pharynx is swabbed out with the pantocain. The patient then swallows the small tube until the cross bar is at the teeth, and from 5-6 c.c. of the pantocain solution are injected. Five minutes later this whole procedure is repeated. This is a highly satisfactory method, and has the advantage of securing the patient's cooperation in swallowing, while the pharynx is anaesthetized. The chief disadvantage is that the pantocain is expensive. Schindler states that if the injection of pantocain into the anesthetization tube is forceful, the pantocain emerges as a spray, and none is swallowed. In our experience however, a small amount of the pantocain is usually swallowed. In the event that a reaction should occur, it is possible that the swallowed pantocain might be incompletely removed by the stomach tube, with aggravation of the reaction. Presumably however, pantocain reactions are too rare to justify this objection, and in any case the risk is less than with cocaine.

The usual method of applying cotton swabs, soaked with a few drops of 10% cocain, to the posterior pharynx is a rapid and satisfactory method. The anesthetization is not for prevention of pain but to abolish the gag reflex. Gagging, of course, disturbs steady vision, and air is lost more rapidly than it can be injected.

As soon as the gag reflex is abolished, the stomach is emptied. An Ewald stomach tube of the same diameter as the instrument is used, in order to test the patency of the esophagus. The patient swallows the tube, and then, by leaning down on a tilted table, allows the stomach to empty by gravity. Mucus and fluid, if left in the stomach, will prevent clear vision.

The patient is now shown the position to be assumed, the left lateral decubitus. The left arm must be under the body. This is highly important because it corrects the sag between the dependent side. The knees are well drawn up, the lumbar spine is bowed convex posteriorly. It is well to spend some time in practice, until the patient can assume the proper position, without being pulled or pushed into place.

INSERTION

The patient being in the proper position, the head holder places his left hand under the head and supports the head with his hand, the right hand merely steadying the head. The little finger of the left hand is used to draw down the lower corner of the mouth. The neck must be limp. The head is slightly extended on the neck and is held so that the face is a little in advance of the neck and chest. The head is dropped slightly so that the right angle of the mouth is in line with the esophagus. As the instrument is advanced down the esophagus, the extension in increased as necessary. It must be remembered by the head holder, that this extension is extension of the head on the neck, not the neck on the chest (the latter movement tending to close the esophagus). The neck is maintained in the plane of the body and slightly flexed. The success of the procedure will frequently depend on the above. The patient must be in the proper position, and he must be relatively relaxed. Almost all of the difficulties of insertion are directly traceable to faulty position and stiffness. The patient's tendency is to extend the neck on the trunk, and to arch the back, two things that invariably put the operator in trouble.

The operator now takes the instrument and rests the metal end in an assistant's hand. This assistant must keep the instrument from bending too far, particularly at the vulnerable point, the juncture or rubber and metal. The gastroscope is held perpendicularly to the body. The operator's right hand holds the flexible part, introducing it over the right side of the tongue, and by bending this portion, gently inserts the tip along the posterior pharyngeal wall, until an obstruction is felt (the crico-pharyngeal constriction). The fore-finger of the left hand is used to keep the tip from being bent down and across the lumen, and to keep the instrument up in the right side of the mouth. At this point two procedures may be followed. The

beginner, or one inexperienced in introducing instruments into the esophagus, had best wait until the patient swallows when he can feel that the slight resistance to the tip has disappeared. After the feel of the instrument has been acquired, he may gently pull forward the base of the tongue, and by very gentle pressure insinuate the tip past the cricoid. In either case it cannot be emphasized too much that if there is an open lumen ahead, and the instrument is not caught by the upper teeth, that no resistance is felt. *Do not push, wait!* If the beginner encounters resistance in any way stubborn, he had best withdraw, and try again another day.

After the cricoid is passed the instrument will slip down the esophagus almost of its own accord until the cardiac pinchcock is reached. Here, in many cases, resistance will be re-encountered. Again the operator must maintain very gentle pressure, and wait until the resistance disappears. Sometimes deep breathing will help. After passing the cardia (approximately when the teeth are at the white mark on the instrument) the tip is in the stomach. The next move is the most crucial. The instrument must be inserted as deeply as possible. In most cases it is necessary to advance until the light connection arm is almost at the patient's lip. This is more difficult than it sounds. Spasm will be encountered which sometimes will be almost impossible to overcome. We have noticed under the fluoroscope, persistent spasm, almost cutting the stomach in two parts. More often however, the resistance is really in the mouth, and can be removed by changing the position of the head slightly, pulling the lip away from the instrument, or by opening the patient's mouth a little more. In any case there is no hurry—one had best be gentle and take his time. Schindler's rule, "Quick insertion, without force," establishes an excellent goal to be reached with increasing skill. A rapid insertion will push the tip to the lower part of the stomach before persistent spasm can appear. In addition, rapidity takes advantage of the first relaxation of the cardia, which is brief and almost coincident with the first swallow. This can be demonstrated under the fluoroscope with barium. However, until one has acquired delicacy of touch, swift insertion is dangerous.

When the instrument has been introduced as far as possible, switch the light on, make certain that the voltmeter registers 8 volts, and then by turning the instrument, try to locate the *angulus*, which will be seen as a fold hanging down across the field. Inflate the stomach very slowly and carefully. When the angulus is found, a deep breath by the patient will reveal the *antrum* beyond. One is now in position to locate the *pylorus*. This is accomplished by watchful waiting, and very slight air inflation. It is usually located during a deep inspiration. Too great an inflation will push the pylorus irretrievably from view.

It is advisable to mention one or two points concerning the location of the pylorus. The rugae, seen running on the floor of the antrum, converge at the rosette shaped pylorus and thus may be used as guides. One must be careful not to confuse a peristaltic wave in the antrum with the pylorus. These waves simulate the pylorus as they sweep down over the antrum.

Remember also that although the first portion of the duodenum sweeps posteriorly, in many cases, the terminal portion of the antrum and the pylorus appear to open anteriorly. In the majority of cases the entire antrum can only be seen by watching a peristaltic wave pass to the pylorus.

The remainder of the stomach is seen by slowly turning and withdrawing the instrument, bringing each portion under observation. Sufficient air is injected to push the mucosa away from the lens. Apparently one need not fear over inflation.

There is no need for hurry, one may take all the time required for complete observation. The light lens is never more than warm, no matter how prolonged the examination. The patients are rarely uncomfortable. They occasionally complain of pain in the mouth or throat, which can usually be relieved by changes in the position of the head. If morphine is not used as preliminary medication, the patients feel the movement of the instrument in the stomach. If too much pressure is exerted, this tactile sensation increases to pain, and is felt just to the left of the mid epigastrium. The pain is promptly relieved by relieving the pressure.

Frequently when one first looks into the instrument, nothing can be seen, not even the light; or only half the field is seen. This means faulty position, and a double curve in the flexible portion. Usually if one reassures the patient, asking him to breathe deeply and relax, this is overcome; if not, readjustment of the neck and body may correct the curve. Occasionally no vision can be obtained and the patient must be brought back another day. The second examination is invariably satisfactory.

ORIENTATION

This is the most difficult technical point in the procedure. It is only by practice and patience that one can be sure of just which area of the stomach is under observation. Each operator must discover this for himself. There are several points however, that may help in learning orientation.

The operator had best take a ruler, or a sheet of paper with suitable marks, and practice observing these through the gastroscope. When this is done several things become apparent, which if unknown, will confuse the observer. Chief of these is that the 80 degree angle of vision gives one a much wider view than expected. It becomes apparent that if the stomach wall be 2-3 cm. from the objective, nearly the whole area between lesser and greater curvature will come into view. The corallary to this is the same point may be observed, even though the instrument be turned through a wide angle. It may be observed, also, that the central portion of the picture is magnified more than the periphery, and that this point is helpful in determining when the object is directly under the ocular. Also, a line on the paper (or a fold on the gastric wall) changes direction with rotation of the instrument depending on the direction of rotation. This may also be used in determining at which point the ocular is directed toward the object in question.

Observation of the paper and marks will reveal that the easiest way for the observer to judge direction, is to picture himself looking out of the objective window, keeping in mind that the patient is on his left side. Then what appears to be toward his left, is to his left, and so forth. Thus with the objective directed toward the anterior wall (as shown by the knob on the eyepiece, which corresponds to the objective) what appears to his left is proximal, what is to his right is distal and so on.

In addition to the above there are several things which help maintain general orientation.

First of these are the outstanding landmarks. The *angulus* which is readily recognized as a veil hanging down over the field, indicates that one is looking at the entrance to the antrum. The *musculus sphincter antri*, which appears to be a fold twisted like a rope, forms part of the anterior boundary of the antral entrance. The "mucus lake" indicates the most dependent portion, usually at the junction of the upper and middle third of the stomach. The *fornix* is seen as a deep recess.

Gradual familiarity with the gastroscopic picture also enables one to place himself fairly accurately. There are certain definite characteristics of each portion. These are not within the scope of this paper, but are recognizable with experience.

POST-INSTRUMENTAL TREATMENT

We have had no reactions of any consequence. One of the first patients complained of severe dyspnoea, and pains in the midthorax, but evidently this was hysteria.

In one or two cases, the examination was followed by epigastric pain. This, however, was apparently due to overinflation, since it was relieved by withdrawing air through a small stomach tube.

Approximately half the cases have a sore throat, varying from slight to moderately severe. More careful handling of the instrument in the throat has reduced the number and severity of these.

Routinely, for the remainder of the day, patients are given only cold liquids. This is probably not important.

It is advisable, in order to alleviate the sort throat, that the patients use a hot salt or mild astringent gargle every one or two hours for the remainder of the day. In addition they are given about a half teaspoonful of dry bismuth subnitrate every two to three hours. The bismuth may coat over and protect any small denuded areas in the throat.

CONCLUSIONS

Gastroscopy is a safe, simple, means of observing the gastric interior. It may be used routinely to examine the gastric interior in order to obtain valuable diagnostic information, that can be secured in no other way.

The detailed description of the technic of insertion is given with a few suggestions in the technic of orientation.

Experimental Study with Certain Tips Used on the Wolf-Schindler Flexible Gastroscope*

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IN the development of gastroscopy it was thought that the construction of a flexible gastroscope would entirely eliminate any dangers arising from the procedure. This proved to be the case until the instrument was modified by the substitution of the sponge tip of Henning for the rubber finger tip previously used on both the rigid and flexible gastroscopes. In several thousand examinations with the flexible gastroscope and rubber finger tip carried out by gastroscopists here and abroad, perforation of the stomach was never observed. In a series of 360 examinations made with the flexible gastroscope and rubber sponge tip we have had three perforations of the stomach, and we know of two others. Hence, we have undertaken a complete investigation of our accidents.

INCIDENCE AND TYPE OF ACCIDENTS

With the rigid gastroscope. Accidents with the rigid gastroscope were reported by Hertel and Kallius (1), Sauerbruch (2), Korbsch (3), Bingel (4), Veillon (5), Schindler (6), Hübner (7), and others. The number of accidents is not known, but it was large. It must be emphasized that all these occurred prior to the invention of the flexible gastroscope in 1932. The lesions were in the esophagus, particularly the lower esophagus. There have been reported only two cases of perforation of the stomach. One (6) was produced by a student who caught the stomach wall between the outer and optical tube of the instrument and caused a tear while withdrawing the gastroscope. Knack (8) observed a perforation of the greater curvature. It is important to note that the danger of the rigid instrument was perforation of the esophagus. In several thousand examinations which have been carried out with the flexible gastroscope *no esophageal lesion has been described.*

With the flexible gastroscope. An investigation of the experience of some other gastroscopists was made. Henning (9), Gutzeit (10), and Moutier (11), each having performed over a thousand gastroscopies with the flexible gastroscope, state that they have had no accidents. Two men (12, 13), however, did report having had accidents. Each had one perforation of

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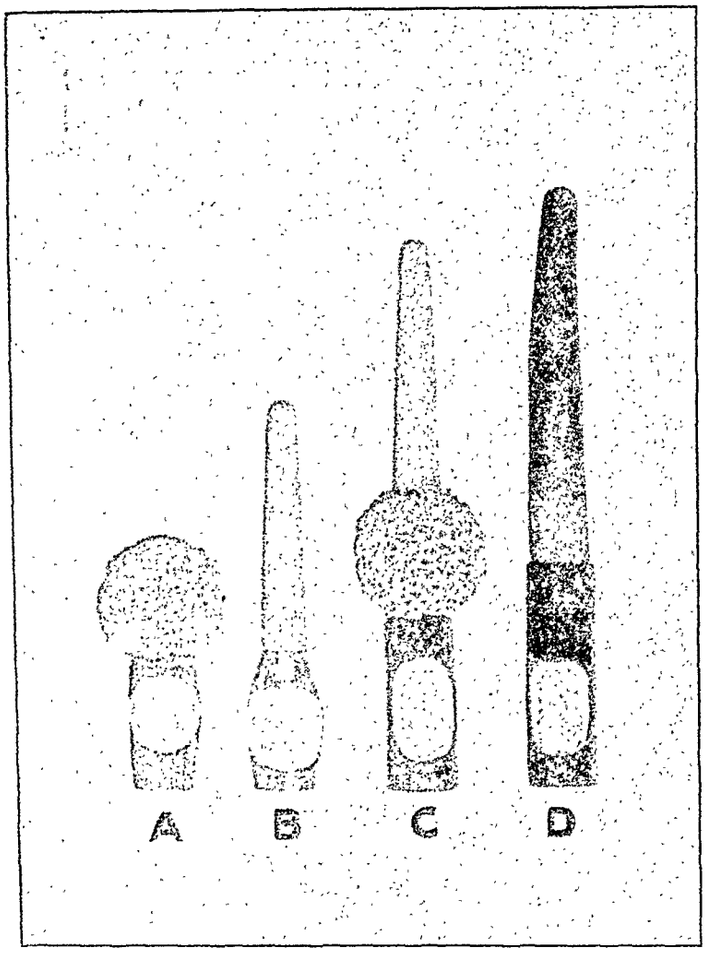


Fig. 1. Types of tips used in this study. (a) is the Henning sponge tip, (b) is the 4 centimeter finger tip, (c) is a combination sponge-finger tip, (d) is a special 6 centimeter tip.

the stomach. In each instance it occurred in a patient with an "apparently normal" stomach and recovery occurred without operation. The diagnosis of perforation was made by the finding of pneumoperitoneum. In an approximate total of 4000 known examinations by the above mentioned gastroscopists there have been but five known accidents. It should be emphasized that none of these accidents involved the esophagus and that *none of them has been fatal.*

POSSIBLE FACTORS INVOLVED

Type of tip. Three types of rubber tips have been used on the flexible gastroscope: the long conical finger (Schindler), the spherical small rubber sponge (Henning), and a combination sponge finger. (Figure 1)

Type and location of lesion. In our cases the gastric lesion proved at operation to be carcinoma. In one case it involved the junction of the upper and middle third of the body producing an hour-glass deformity. The cardia was not involved. In the other two cases a considerable portion of the lesser curvature was involved.

Site of perforation. In all of our cases the perforation was through an uninvolved portion of gastric wall, not through the tumor. Two were high in the posterior wall, and one was in the anterior wall near the greater curvature.

Condition of the gastric wall at the site of perforation. The operative report described the gastric wall of two cases as "definitely more friable than one would consider normal." In Case 3 "it may not have been quite as resistant as the normal wall usually is, but the difference was not marked, and the sutures held as in the normal stomach wall." No sections were made in the first case. The tissue removed from the edge of the perforation in Cases 2 and 3 contained only mucosa and submucosa, which were normal; but we can say nothing of the condition of the muscular layers.

Mechanism of perforation. In two cases the peritoneum was definitely seen. The perforations were due to the tip and not to the distension with air.

CAUSES OF PERFORATION

Were contraindications present? In Case 1 there was a known hour-glass deformity which was not considered a definite contraindication and even now it is not if the proper type of tip is used.

In the second case roentgen examination did not show any carcinomatous involvement of the cardia or esophageal hiatus. The Ewald tube was easily introduced into the stomach. It cannot be said that there

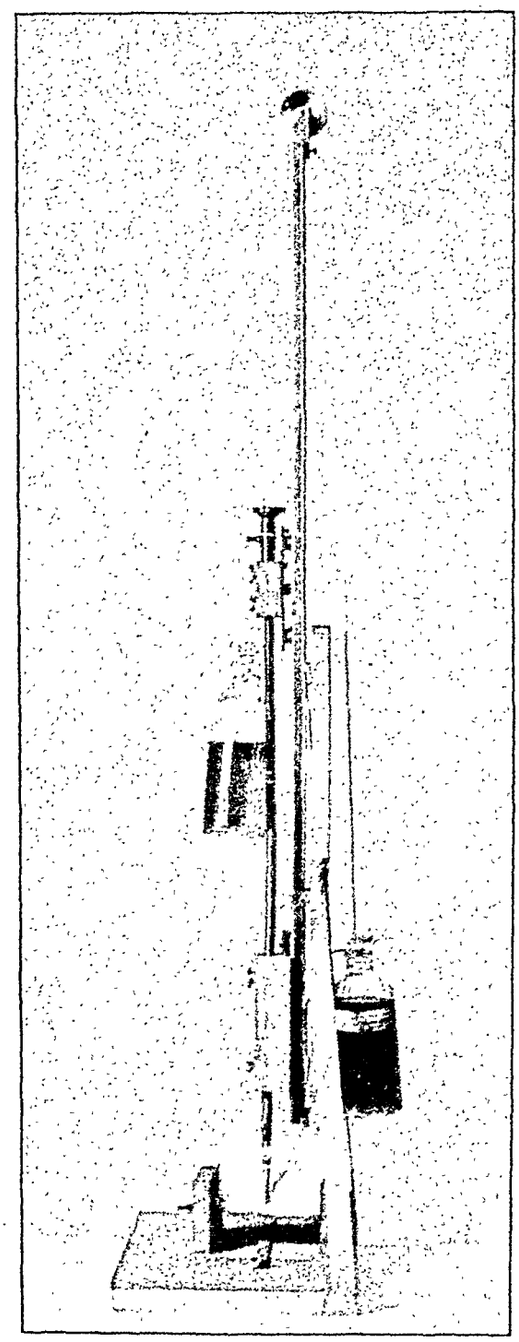


Fig. 2. Apparatus with gastroscope in place.



Fig. 3a. Finger tip in a loosely suspended stomach. Note the gentle curve of the tip and the slight curve of the instrument.



Fig. 3b. Sponge tip in the same stomach. Immediately ahead of the sponge the mucosa is heaped up. The tip is beginning to push out a pouch and stretch the mucosa above it. The instrument is not curved or bent.

were contraindications present in this case. Case 3 was done to check the X-ray diagnosis of a polyp of the cardiac portion of the stomach. It seems that this was a definite indication for gastroscopy and not a contraindication. Again it should be recalled that none of the perforations was through tumorous tissue.

Friability of the gastric wall. The fact that in Case 3 the gastric wall was not definitely friable and the fact that the other reported accidents (12, 13) occurred in normal stomachs argues that friability is not a sole factor in causing perforations.

Elasticity of the instrument. Experience has proved that the present instrument has the proper flexibility to prevent esophageal lesions and still permits excellent visualization of the stomach.

Angle of impingement on posterior wall. The flexible gastroscope strikes the posterior wall at approximately the same angle that the rigid instrument did—about thirty degrees.

The role of the Assistant. In our series all the accidents occurred while an inexperienced assistant was holding the head. An inexperienced assistant may render the examination difficult and unsatisfactory.

The speed of the introduction of the instrument. In our series the perforations occurred, not when the instrument was moving rapidly but when a "slight resistance" was felt and movement was slow. However, the old rigid instruments were frequently introduced slowly, and yet they did not perforate the stomach.

To demonstrate experimentally the effect of the velocity of the instrument we made repeated observations in the following manner:*

A dog stomach was first stretched tightly in the frame and placed at an angle of thirty degrees to the horizontal. The instrument, which was not counterbalanced, was allowed to fall of its own weight from different heights. The results were always the same: both tips slid rapidly over the membrane to the farthest edge, thereby bending the lower part of the gastroscope. Both tips slid easily when the stomach was suspended loosely in the frame, but the sponge tip occasionally stopped before it had gone the full length of the membrane. This sliding may be explained by two facts. First, if the instrument is passed rapidly, the inertia of the stomach wall changes none or little at all before the tip has passed over any particular area. Second, by the time the inertia of the stomach has changed the flexible part of the instrument is well into the stomach, permitting the instrument to bend readily. *The friction between the tip and the gastric wall.* A dog stomach was placed at an angle of thirty degrees with the horizontal. The instrument was exactly counterbalanced. The tip was gently placed in contact with the uppermost part of the membrane. Water was slowly added to a bottle on the carriage. It was run in from a burette with a long rubber tube which extended to the bottom of the bottle so as to avoid any inertia caused by the fall of water. The end result was considered to be the weight of water necessary to cause the tip to slide the full length of the membrane. There was a relatively constant weight which caused the rubber finger to suddenly slide the full length. Once movement was initiated the tip slid easily and rapidly. With the sponge tip, however, it required approximately 100 grams more to initiate sliding which was jerky.

Table I shows the characteristic results using the sponge tip, a combination sponge and finger, a four centimeter long finger, a six centimeter finger, and a short (2.5 centimeter) finger. It is apparent that the sponge tip creates more friction than the rubber finger or even the combination sponge finger. Each test was carried out as quickly as possible to avoid changes in the membrane, elasticity, tension, and moisture.

TABLE I

Finger Tips Gms			Sponge-finger tips	Henning sponge tip
6 cm.	4 cm.	2.5 cm.	Gms.	Gms.
355	338	344	417	665
340	345	370	500	530
335	330	405	420	540
340	375	385	440	530
330	340	390	435	515
315	335	360	410	490

Foot Note Description of apparatus. (Figure 2). The apparatus consisted of a metal upright on a baseboard. The upright was slotted to carry a roller attached to the wooden block, which served as a carriage for the gastroscope and could be easily moved up and down. There was a pulley at the top of the upright so that weights could be attached to a cord and exactly counterbalance the gastroscope and the carriage. At the lower end of the upright was a fixed wooden block through which the gastroscope passed. Below this, on the baseboard, was a frame on which the test membrane was placed and which could be fixed at any point at any angle. Dogs' stomachs were used as test membranes. Some were fresh, others were preserved in 30% glycerine in physiological saline at ice-box temperature to keep them soft and pliable

The transmission of pressure. Finally the question of how the tip transmitted the pressure exerted on the gastric wall by the advancing instrument was considered. This time the entire stomach was suspended loosely, so that the gastroscope passed over the posterior wall. The finger tip slipped easily over the mucosa, whereas the sponge tip "skidded" along the

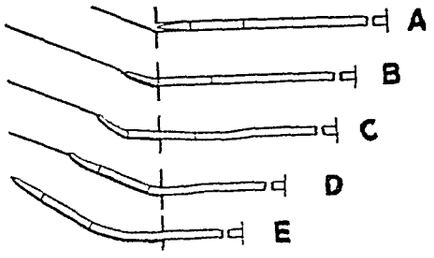


Fig. 4. Diagramatic lateral view of gastroscope as it passes through the esophageal hiatus and along the posterior wall of the stomach. (a) finger tip at the cardia, (b) first contact with the posterior wall, (c) instrument slightly curved from tip through lower portion in esophagus, (d) tip guiding instrument over posterior wall. Note curve of gastroscope, (e) gastroscope advanced to lower depths of the stomach.

surface. Because of the friction between the sponge tip and the stomach the sponge was rolled under itself. The mucosa behind the advancing sponge was stretched tightly, while folds of tissue were piled up in front of it. Many times there was so much tissue piled up in front of the sponge tip that it was impossible to pass over (Figure 3). In these instances the sponge tip pushed out a deep pouch and finally the instrument "buckled," but the tip did not turn upward and slip out of the pouch. When the gastroscope with a finger tip was passed into such stomachs the finger followed down one side of the pouch and curved up the other side until it slipped over the edge (Figure 4).

COMMENT

It is advisable to appraise diagnostic procedures from time to time. Gastroscopists believe that gastroscopy is as safe a procedure as passing an Ewald stomach tube. We are of the same opinion.

It seems that the outstanding factor operative in our accidents was the use of the sponge tip. A rubber finger tip acts as part of the flexible system of the gastroscope. Immediately proximal to the tip is a seven centimeter rigid part consisting of the rubber finger receptor, the lamp, and the objective. Proximal to this part is the main flexible portion of the gastroscope containing the lens system. As the tip protrudes through the esophageal hiatus, the under surface of the finger tip contacts the posterior wall as shown in Figure 4a. As the tip descends a little further, one has the condition represented in Figure 4b. The pressure is increased, but the rubber is pliable enough so that the finger bends easily. As the instrument descends further and more of the finger tip contacts the posterior stomach wall, the resistance or pressure of the stomach increases and the effect of the elasticity of the rubber finger is greater, so that there is a tendency for the upper part of the flexible system to bend very slightly in the lower esophagus (Figure 4c). Finally, the elastic effect is enough to bend the instrument at the junction of the rigid and flexible part as shown in Figure 4d. When the instrument bends at this point, the flexible portion above is slightly curved. The full length of the finger now lies on the stomach wall and slides easily. The finger directs the instrument and initiates an early bending of the upper flexible portion. This results in an increasing surface of contact between the gastroscope and stomach wall as the instrument advances (Figure 4e).

When the sponge tip is used, the first seven centimeters of the instrument are rigid. The vital difference between the sponge and finger tip is apparent. There is no *flexible part* of the instrument in the stomach until seven centimeters have passed the hiatus. There is *nothing* to deflect the sponge tip (Figure 4c). *The entire pressure is always exerted on the very small surface of the stomach wall in contact with the sponge tip.* The tendency is to push out a deep pouch (Figure 4d). The pressure phenomena are exaggerated by the sponge tip because it prevents the instrument from sliding easily. No one will question the fact that an old smooth tire will skid much easier than a new one with a good "non-skid" tread. Likewise, if we used a smooth ball tip instead of a sponge, the former would slide easier than a "non-skid" sponge *but not so easily as a* finger tip which readily adapts itself to any change in contour and follows the course of least resistance. Furthermore, a ball tip would still be objectionable because it cannot direct the instrument nor alter the pressure any better than a sponge tip.

CONCLUSIONS

Evidence is presented to show that the addition of the sponge tip to the Wolf-Schindler flexible gastroscope was a modification which rendered the instrument unsafe. This is in part the result of a "non-skid" effect. The friction between the sponge tip and the stomach wall is greater than with a long rubber finger tip of moderate elasticity and flexibility.

A long rubber finger directs the instrument in the line of least resistance and initiates bending of the flexible portion thereby distributing pressure more evenly. A sponge tip does not deflect the instrument nor does it facilitate its bending and thus the pressure of the advancing gastroscope is localized to a small point beneath the sponge tip.

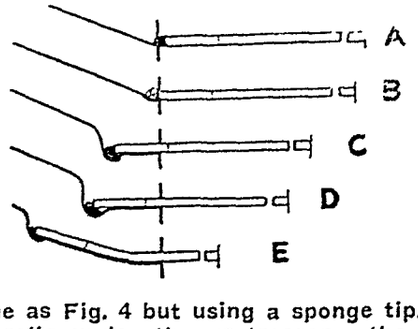


Fig. 5. Same as Fig. 4 but using a sponge tip. Note how the sponge rolls under the gastroscope, the deep pouch that is pushed out, and that the instrument does not bend until the final stage.

We believe that gastroscopy is a safe and harmless procedure if a few simple precautions are observed. Furthermore, we believe it is essential that one use a rubber finger tip four to six centimeters long.

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Chronic Hypertrophic Ulcerative Gastritis Treated by Coutard's Method of Roentgen Therapy: Case Report with Unusual Course and Result

By

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THE following discusses a case of chronic hypertrophic gastritis treated by Coutard's method of protracted high voltage roentgen therapy, demonstrating the results on the chronically inflamed gastric mucosa. The patient was observed over a period of twelve years (1922-1934). During this time he submitted to 65 gastroscopic examinations; 64 of these were performed from 1929 to 1934. The roentgenologic treatment was given in 1932. The gastroscopic observations were made not only by myself but were checked by more than 100 physicians who were participating in gastroscopic courses. Among them were gastroenterologists of world-wide reputation.

CASE REPORT

The patient was a man, born in October, 1875. Since the World War, he had complained of continuous gastric pain which was not relieved by rest in bed, food or alkalies. Because of this pain he applied for a war pension to which he was entitled, according to German law, if disease diminished his ability to work by 30 per cent or more.

Thorough examination in the military hospital of Munich showed no pathologic findings. The patient appeared thin, but the internal organs were normal. Stomach content after Ewald meal contained normal amounts of free and total hydrochloric acid (44 62). No increase of cells was found. Roentgenologic examination of the stomach was entirely negative. There was no occult blood in the stools. It may be assumed that there was no change in these negative findings until the beginning of the Roentgenologic treatment in 1932. Since the military hospital had found that gastroscopy was able to reveal definite pathologic changes in cases in which usual methods had given no results at all, the patient was referred for gastroscopy in 1922.

Gastroscopy was performed with the Schindler rigid gastroscope of 1922. It was not possible to see either the antrum or the pylorus. Only the upper parts of the body of the stomach were observed. These showed very marked changes. The mucous membrane was swollen, velvety, hypertrophic and on the posterior wall three superficial distinct erosions were observed.

The *diagnosis of a marked chronic hypertrophic ulcerative gastritis* was made and the patient received his pension.

He was not examined gastroscopically again until August, 1929. At this time he reported to me that he had never been relieved of his symptoms and that he was completely unable to work. From this time until the invention of the flexible Wolf-Schindler gastroscope, the patient had 16 gastroscopic examinations. The principal findings at each examination were similar. The swollen, velvety, porous character of the mucous membrane of the stomach was exactly the same as in 1922. Only at one examination was it possible to see the antrum and pylorus. The swollen mucosa of the body almost always contained several ulcerations at different sites in the anterior wall, in the greater curvature or in the posterior wall. The erosions were generally yellowish, sometimes white and very shallow. Frequently mucosal hemorrhages, varying in size, were seen.

An unusual feature of this case is that the picture did not show the usual improvements and relapses encountered in this disease, but the condition remained essentially unchanged. The patient said that he was suffering continuously, and he finally received a pension of 100 per cent.

The condition appeared much worse than that of a true gastric ulcer, although in 1932 I had the impression that one of the erosions was so deep, regularly defined and round that the transformation of a gastritic ulceration into a true gastric ulcer seemed evident. However, this was not so. Gastroscopy performed one week later proved that this ulcer had disappeared completely while other superficial erosions had been formed at different sites.

From May, 1932 on, the patient was examined with the flexible Wolf-Schindler gastroscope. With this instrument the antrum and pylorus were always visible. There were also hypertrophic changes, but these were much less marked than in the upper body of the stomach. During this time the patient was treated with rest in bed for many weeks, a bland diet, often merely a liquid diet, hot applications, lavages, intravenous injections of protein bodies, alkalies, charcoal, bismuth, barium, silver, etc. None of these definitely improved the condition.

At that time (1931) Sielmann (Munich) and I had begun to treat selected carcinomas of the stomach with Coutard's method of high voltage X-ray therapy. It is well known that with this type of therapy one tries to destroy tumor cells in the stage of mitosis and finally to kill all cells of the tumor. This therapy causes a very severe "burning" or inflammation of the skin as well as the mucous membrane. When the irradiation is discontinued the in-

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flammation regresses and regeneration of the burnt tissues is observed. The astonishing results need not be discussed in this connection. We had observed this picture not only in cancers of the mouth but also in the gastric mucosa during the treatment of stomach cancers. Therefore I conceived the idea of treating this hopeless case of hypertrophic, ulcerative gastritis in the same way, in order to "burn" the mucous membrane of the stomach and to start its complete regeneration. The patient was told of the uncertainty of this treatment, of the disagreeable incidental effects and of the strain; but since he was suffering from terrific pain constantly he consented without hesitation to undergo the treatment.

Gastroscopy at this time disclosed velvety, swollen mucosa of the whole stomach, numerous very short, extremely stiff folds especially in the anterior wall, numerous small, mucosal hemorrhages and flat yellowish erosions. Two sickle shaped, sharp folds crossing the greater curvature of the body were seen which were again demonstrated in many examinations. Apparently these were caused by fibrous, inflammatory changes of deeper layers of the stomach wall. Some of these changes were photographed with Henning's photographic camera through the rigid gastroscope. The acidity of the stomach contents after Ewald meal was normal. Repeated and very carefully performed X-ray "relief" exposures with controlled pressure failed to demonstrate either the small, stiff folds or the high, sharp folds crossing the greater curvature. These latter two folds were still observed until June, 1934. All Roentgenologic attempts to demonstrate these most outspoken alterations of the mucosal "relief" were in vain.

Coutard's method of high voltage X-ray treatment was performed daily for 45 days. The patient had the usual skin reaction in this type of treatment. He felt very weak but it was not necessary to hospitalize him.

Results of Treatment: Emptying of the stomach before gastroscopy in the second half of the treatment disclosed pus like secretion. Gastroscopically, the mucosa was covered with thick layers of mucus and pus; consequently, nothing could be told from the appearance of the mucosa. Four weeks after the treatment had been discontinued, the mucosa became visible again. Pus and mucus had disappeared completely and at this time, *for the very first time in over ten years a normal mucosa was seen. The velvety swollen character had disappeared completely, the small stiff folds were gone and no ulcerations were present.* The mucosa appeared smooth, glistening, silk-like, similar to that of a healthy individual. Only the two sickle shaped folds crossing the greater curvature recalled the fact that this stomach had been severely diseased.

The patient was free of pain for the first time since the end of the World War. This picture remained unchanged for one year until the end of 1933. At that time, the mucosa above the sickle shaped folds began to look a little grayish. Repeated gastroscopies showed that the grayish area increased in size, the mucous membrane became thinner, and finally in December, 1933, distinct blood vessels were seen. A definite *atrophic gastritis* developed. At the same time the patient began to feel exceedingly nervous. His eldest son stated that living with the father had become very difficult because the father was so irritable. The patient himself complained of irritability, of extreme weakness, of epigastric pressure with gas and eructation. However, this discomfort was not comparable with the former condition of continuous pain.

At this time the observation was interrupted and, since no further data is available, it has seemed advisable to report this most unusual case at this time. A short time ago I received word from this patient that his condition was unchanged.

COMMENT

Chronic, hypertrophic gastritis is a frequent and always severe disease. It is found in about 12 to 13% of all patients who have gastroscopic examinations. From 1922 on, I have seen about 340 cases. Many of these have been followed clinically and gastroscopically for months or years. A complete cure has never been observed in the usual course of the disease, but ulcerations occur only occasionally and in the form of attacks. These heal quickly with a bland diet.

The patient above described is unique because of the obstinancy of the presence of ulcerations which were observed for three years, and which had probably been present for ten years. However—and this fact is remarkable theoretically—none of them developed into chronic gastric ulcers. The severe, painful disease could be diagnosed only gastroscopically. All other methods, especially the X-ray "relief" technic, showed no evidence of the disease. The most marked changes of the mucosal "relief" could not be demonstrated by Roentgenologic examination.

After 10 years of unsuccessful therapy, 45 treatments with Coutard's method of high voltage X-ray therapy were given. The idea was to destroy the diseased mucosa and to cause subsequent regeneration. We succeeded completely with this procedure. After a primary, severe purulent, acute inflammation, the gastric mucosa became normal for the first time in ten years. The patient recovered and remained in good health for one year when atrophic gastritis developed. This form of gastritis is, in my experience, never seen as a result of hypertrophic gastritis. No sign of atrophy was observed in the case under discussion before the beginning of Roentgen therapy. Therefore, we feel sure that this atrophic gastritis was caused by that therapy. Although the usual symptoms of atrophic gastritis developed—nervousness, epigastric pressure, gas and eructation—the condition of the patient was much improved when compared with the extreme pain before the beginning of Roentgen treatment.

Since we were able to observe this patient long enough to witness the development of the atrophic gastritis, we are unable to recommend Coutard's method of high voltage X-ray therapy as a routine measure in this disease. We believe that it should be restricted to the few hopeless cases which have been observed gastroscopically over long periods, in which ulcerations have always been found later and which could not be improved by the usual therapeutic procedures.

SUMMARY

1. A patient suffering from severe hypertrophic ulcerative gastritis was observed over a period of twelve years.

2. The diagnosis could be made only with the use of the gastroscope; X-ray relief technic did not demonstrate the very marked changes of the mucosal relief. Sixty-five gastroscopies were performed.

3. The usual improvement seen in this disease was not observed in this case. Ulceration and extreme pain were present without interruption.

4. In spite of protracted, careful observation, development of a gastritic ulcer into true gastric ulcer was not seen.

5. Coutard's method of high voltage X-ray therapy caused severe, acute, purulent gastritis and subsequent regeneration of an essentially normal mucous membrane. This picture was seen for one year. The patient seemed to be cured when atrophic gastritis developed as a late result of the therapy.

6. Roentgenologic therapy by Coutard's method can be recommended only for the most severe cases of hypertrophic ulcerative gastritis which have been observed gastroscopically over long periods and which fail to respond to the usual methods of therapy (diet, rest in bed, lavage, silver, alkali, etc.).

SECTION II—*Experimental Physiology*

The Proteolytic Effect of Normal Gastric Juice on Beef Muscle Globulin, with Reference to the Reported Action of the Anti-Anemic Intrinsic Factor

By

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CASTLE and his coworkers (1, 2, 3, 4) demonstrated that when normal gastric juice and beef muscle were incubated together a substance was produced which was therapeutically active in pernicious anemia. The factor in normal gastric juice he called "intrinsic factor" and the substance upon which it acted he termed "extrinsic factor." He found that the globulin of beef muscle contained the extrinsic factor. Griffiths (5) made a study of the chemical aspects involved in this process, using the beef muscle globulin as a source of the extrinsic factor. This investigator compared the proteolytic effect of normal gastric juice and gastric juice from patients with pernicious anemia —that is, gastric juice presumably devoid of intrinsic factor. This comparison was made on the basis of the production of nitrogenous material not precipitated by trichloracetic acid. There was found to be a small amount of soluble nitrogen produced as a result of incubation at pH 6 which he could not ascribe to the action of pepsin or trypsin and which, on the average, was greater in the case of normal gastric juice than in juice aspirated from persons with pernicious anemia. Griffiths suggested that this production of soluble nitrogen might be related to the action of the intrinsic upon the extrinsic factor.

Using liver extract as a substitute (6), we were unable to demonstrate a change in the nitrogenous components of the liver extract which could be attributed to any other factor than pepsin. Since Griffiths reported a measurable increase in soluable nitrogen when he used beef globulin as a source of the extrinsic factor, we undertook to perform certain experiments based on those described by him, but involving certain additional controls.

*From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis, Indiana.
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EXPERIMENTAL

Beef muscle globulin, the source of the extrinsic factor in these experiments, prepared according to the method described by Castle (3), was dried in a vacuum desiccator and powdered. Normal gastric juice was obtained (following histamine stimulation) from young, healthy adults, all of whom from clinical experimental work had been shown to secrete gastric juice containing the intrinsic factor. The material thus obtained was filtered clear and kept in a refrigerator until used. Samples containing bile were discarded. The boiled gastric juice employed in control experiments was filtered free of coagulum.

In the first series of experiments the technique employed was similar to that described by Griffiths (5), but with a few modifications. One hundred milligram portions of beef muscle globulin were incubated for three hours at 40° C. with the equivalent of 4 c.c. of gastric juice, boiled and unboiled, at pH 2 (approximate) and pH 6.0. To the incubation mixtures were then added 4 c.c. of 25 per cent trichloracetic acid. Following overnight refrigeration at 0° C. these were filtered clear and the nitrogen content of the filtrate determined.

The incubation mixtures were prepared as follows: To 10 c.c. of gastric juice, boiled and unboiled, possessing a known titratable acidity, were added 10 c.c. of N/10 HCl in the case of the pH 2 mixtures, 10 c.c. of N/10 phosphate buffer in the case of the pH 6 mixtures, an amount of NaOH equivalent to the total acid of the gastric juice in the case of the pH 6 mixtures, and to each was added distilled water in sufficient quantity to bring the volumes to 25 c.c. Of these solutions, 10 c.c. were added to 100 mg. of muscle globulin and 10 c.c. placed in an empty tube for control purposes. One drop of toluene having been added in each case as a preservative, all the tubes, tightly stop-

pered, were placed in a rotary shaker and agitated for 3 hours in a water bath maintained at 40° C.

The nitrogen content of the filtrates was determined according to the manometric method of Van Slyke (7) as modified by Van Slyke and Kugel (8).

CALCULATION OF RESULTS

To determine the true change (C) in soluble nitrogen resulting from incubation at each pH, the value obtained for the globulin incubation mixture containing the boiled gastric juice was subtracted from that containing the unboiled, and from the value (G) thus derived was subtracted the difference in soluble nitrogen (G. J.) between the solutions of the same pH containing the boiled and unboiled gastric juice. The results were calculated on the basis of 100 c.c. of gastric juice.

From the results shown in Table I it appears that in each case incubation at pH 6 led to an increase in the soluble nitrogen of the globulin incubation mixture. The following possible explanations suggest themselves: (1) proteolytic action of the intrinsic upon the extrinsic factor; (2) proteolytic action of pepsin upon the beef muscle protein; and (3) differences in absorption upon the beef muscle globulin of soluble nitrogenous substances in boiled and unboiled gastric juice.

That appreciable peptic action may take place at pH 6 was considered likely in view of the fact that in every case where the rennin content of gastric juice at this pH was determined such activity was demonstrated. In order to test this hypothesis, beef muscle globulin was incubated with pepsin solution (U. S. P. Pepsin 1:3000) at pH 6 under precisely the same conditions employed in the preceding experiments. The concentration of the pepsin solution was adjusted in such a way that its rennin content (determined according to the method employed by Helmer, Fouts, and Zerfas (9)) approximated that of the gastric juice used in the preceding experiments. The results are expressed in Table II and are calculated on the basis of 100 c.c. of pepsin solution.

From the figures shown in Table II it is apparent that at least a part of the increase in soluble nitrogen obtained on incubation of gastric juice and beef muscle globulin at pH 6 may be due to peptic proteolysis. Failure to obtain the same degree of soluble nitrogen change using pepsin solution possibly indicated an independent action on the part of the intrinsic factor of the gastric juice, but we felt that it might also be correlated with the numerous dissimilarities in physical and chemical properties existing between the normal and artificial gastric juices. It was therefore decided to rule out, if possible, peptic activity at pH 6 by employing as a substrate beef muscle globulin which had been predigested with pepsin.

Beef muscle globulin was digested 8 days at 40° C. with one-half its weight of pepsin in N/10 HCl, toluene having been added as a preservative. The solution was then neutralized with NaOH and evaporated by distillation in vacuo, the pH being maintained at approximately 6.5 during the process. The residue was dried in a vacuum desiccator and powdered. An amount of this material equivalent to 100 mg. of the original beef muscle globulin was incubated 3 hours with 10 c.c. of gastric juice solution at pH 6, prepared as described above. Four cubic centimeters of 25 per cent trichloracetic acid were then added and, following overnight refrigeration, the nitrogen content of the filtrate was determined. It was found that boiled gastric juice served as a most unreliable control, since, on boiling, hydrolysis apparently takes place the products of which are adsorbed on the substrate and precipitated by trichloracetic acid to a variable extent. For this reason a control was devised as follows: To an amount of digested beef globulin equivalent to 100 mg. of the original material were added 4 c.c. of trichloracetic acid and then 10 c.c. of the gastric juice solution at pH 6. Following refrigeration, nitrogen was determined on the filtrate. No change in soluble nitrogen occurred as a result of incubation with normal gastric juice at pH 6.

In order to determine the possibility of a proteolytic action not demonstrated by an increase in soluble nitrogen under these conditions, the Willstätter and Waldschmidt-Leitz (10) titration technique was ap-

TABLE I

Changes in soluble nitrogen following incubation of normal gastric juice with muscle globulin (G), and alone (G.J.). Net change (C.) = G. — G. J.

		Mg. Change per 100 c.c. Gastric Juice Solution					
		pH 2 (approx.)			pH 6.0		
Experiment	Titratable Acidity of Gastric Juice (c.c. N/10 NaOH per 100 c.c. G. J.)	G.	G. J.	C.	G.	G. J.	C.
1	90	272.6	3.1	269.5	9.6 ± 0.5*	— 1.6 ± 0.5	11.2 ± 1.0
2	95	290.0	6.5	283.5	6.1 ± 0.8	0.0 ± 0.2	6.5 ± 1.0
3	130	280.9	4.7	276.2	5.0 ± 0.3	— 0.6 ± 0.1	5.6 ± 0.4

* = probable error.

TABLE II

Changes in soluble nitrogen following incubation at pH 6.0 of pepsin solution with muscle globulin (G), and alone (P.). Net change (C.) = G. — P.

Experiment	Composition of Pepsin Solution	Mg. Change per 100 c.c. Pepsin Solution		
		G.	P.	C.
1	0.6 gm. pep. 1:3000/100 c.c.	3.3	0	3.3
2	0.8 gm. pep. 1:3000/100 c.c.	1.3	— 1.9	3.2

plied in the following manner. Predigested globulin material was suspended in water in such concentration that 1 c.c. contained the equivalent of 18 mg. of the original beef muscle globulin. Sixteen cubic centimeter portions of this suspension were incubated for 3 hours at pH 2 and pH 6 with 12 c.c. of gastric juice (the acid and alkali required to adjust the pH being contained in 4 c.c. of solution added to the incubation mixture). Following incubation and refrigeration, 1 c.c. samples were titrated in 97 per cent alcoholic suspensions with N/50 NaOH dissolved in 97 per cent alcohol; 5 c.c. samples were titrated in 50 per cent alcoholic suspensions with N/10 NaOH in 50 per cent alcohol. Phenolphthalein (1 c.c. of 1/10 per cent) served as the indicator. Direct color matches between the incubated samples and their controls were obtained. The latter were prepared as follows: The globulin suspension, gastric juice, and pH-adjusting solution were added together at refrigerator temperature, in the same proportion as described above, and 1 c.c. and 5 c.c. aliquot portions of the mixture were immediately pipetted into alcohol. These alcoholic suspensions, containing 97 per cent and 50 per cent alcohol, respectively, were titrated as above. No differences in titration values between the incubated samples and their controls were observed at either pH.

DISCUSSION

The foregoing experiments, using a beef muscle preparation as a source of Castle's extrinsic factor, failed to demonstrate any extra-peptic proteolytic activity in normal gastric juice. It is obvious that these results are not conclusive evidence against the possibility of such activity. For example, the quantitative aspects may be such that the limits of error of the methods employed overshadow the chemical changes sought. So far as the results of the trichloracetic acid precipitation method are concerned, it must be borne in mind that nitrogenous compounds, which alone are not precipitated by trichloracetic acid, may be so precipitated, in part at least, if adsorbed on other proteins present in the mixture. This circumstance appears to account for the fact that occasionally there are marked differences observed between the soluble nitrogen content of boiled and unboiled gastric juice when these are analyzed alone, which are not discoverable when the gastric juices are analyzed in combination with their protein substrates. Such variable behavior on the part of boiled and unboiled gastric juice can render controls uncertain and results dubious.

The experiments involving predigested protein are free from certain of these objections; on the other hand, it is not inconceivable that prolonged incubation of the extrinsic factor with pepsin may lead to its destruction or, at any rate, attenuation. This is considered unlikely in view of the reported stability of the extrinsic factor (11, 12), but it must be considered as a possibility.

The Authors feel that some of the results published by Griffiths may represent physical and chemical processes unrelated to protein hydrolysis, peptic or otherwise. Thus, this investigator reported an increase in soluble nitrogen at pH 2 in the case of gastric juice from patients with pernicious anemia amounting to almost one-third that produced by normal juice, although the data reported by Helmer, Fouts, and Zerfas (9), who studied the gastric secretions of 47 patients with pernicious anemia following histamine stimulation, indicated that the gastric juice contains, on the average, less than 1/100 the normal amount of pepsin.

The disparity between our results and those obtained by Griffiths may be related to the differences between the physical and chemical properties of boiled and unboiled gastric juice mentioned above, which differences would, from a theoretical standpoint, be greater in the case of unfiltered than of filtered gastric juice, and would be especially noteworthy in the case of gastric juice from patients with pernicious anemia, since the mucus content of such gastric juice is very high.

SUMMARY

Efforts have been made to account for the increase in soluble nitrogen obtained by Griffiths on incubating gastric juice containing Castle's intrinsic factor with beef muscle globulin, a source of extrinsic factor.

The results of these experiments fail to support Griffiths' contention that peptic activity at pH 6 can be disregarded, and render doubtful his conclusion that at this pH, proteolytic activity, measurable by the methods employed, is possibly due to the antianemic intrinsic factor of normal gastric juice.

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The Changes within the Cells of the Gastric Mucosa During Secretory Activity*

By

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THIS study was undertaken in order to correlate the morphological variations of the secretory cells of the gastric glands with stages of functional activity. The detailed analysis of the changes of the known cytoplasmic and nuclear elements will be reserved for a later publication. The discussion is limited to the mitochondria and Golgi apparatus and to the cellular secretory products, such as pepsinogen granules and mucus.

The cycle of events within the cells could be most clearly demonstrated only by active stimulation. In the experiments to be described pilocarpine hydrochloride was employed because of its stimulating action on the mucosa of both the corpus and antrum. The stomachs of the animals studied did not show any pathologic changes and in the longer experiments returned to the phase observed in the controls.

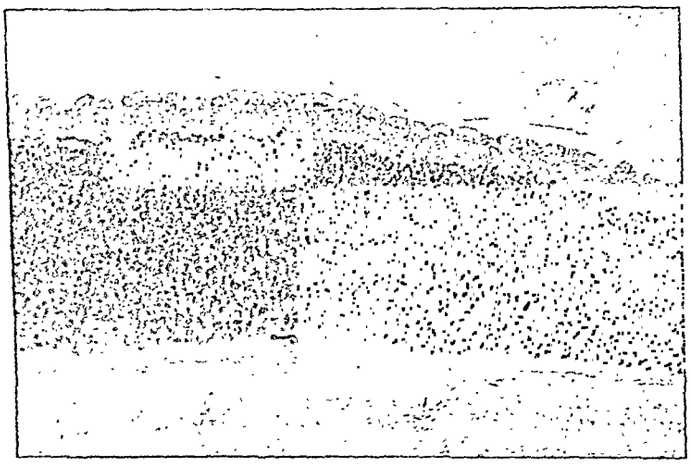


Fig. 1. Fundus. Fed control animal. Uniform character of acid cells. Regaud: Altmann's acid fuchsin. (Low power).

METHOD OF STUDY

Young white rabbits of approximately the same weight were used for the experiments. Four of them belonged to the same litter, three to another. The animals were injected intramuscularly with 12.5 mgs. per kilogram of freshly prepared 1% aqueous solution of pilocarpine hydrochloride. Following this they received no food but were given small amounts of water. Two types of control animals were used. One was fed until the time of the experiment; the other was sacrificed after starvation for 27 hours. The pilocarpine hydrochloride was administered to animals which had been allowed to feed until the time of injection. They were sacrificed at various intervals thereafter. The stomach was immediately removed and the contents collected for acid and pepsin determinations. The tissue was placed into various fixatives for cytological study within twenty minutes after the death of the animals. The major portion of the gastric mucosa was frozen over carbon dioxide ice and extracted for acid and pepsin content.

*From the Laboratories of The Mount Sinai Hospital, New York City. Aided by a grant from Dr. A. A. Berg.
Submitted August 3, 1936.

OBSERVATIONS

In the fundus of the control animal starved for 27 hours the peptic or chief cells of the chief glands are filled with large, round secretory (pepsinogen) granules which occupy the entire cytoplasm and obscure the nucleus. The mitochondria can hardly be identified although short filaments are seen at the base of the cells. The pepsin content of the mucosa determined quantitatively is very high. The cells in the basal portions of the glands are more packed with granules than those in the superficial portions. In the corpus, however, the granules, although numerous, fill only the half of the cell near the lumen. The mitochondria form short, narrow filaments in the basal portions of the cells and extend to the region of the granules. The parietal or acid cells in both the fundus and the corpus contain numerous round granules uniformly distributed throughout the cytoplasm. These granules are smaller than the pepsinogen granules and possess different staining characteristics. The nature of the granules of the acid cells cannot be definitely stated at present.

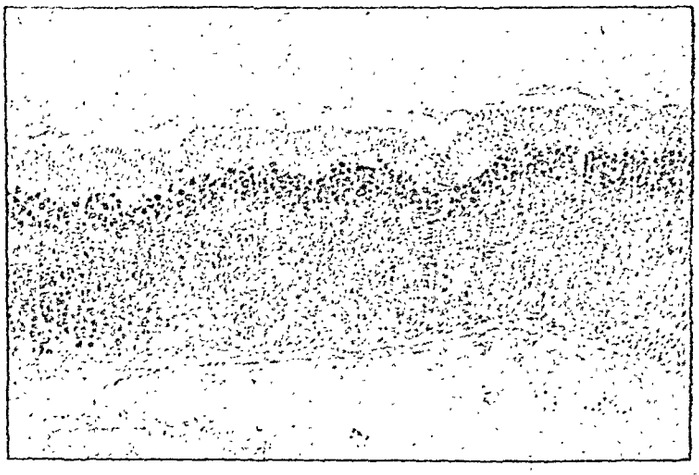


Fig. 2. Fundus. One hour after injection of pilocarpine. Acid cells basal to the neck portions of the chief glands contain less granules. Granules stain less intensely. Regaud: Altmann's acid fuchsin. (Low power).

In the second control animal which was fed until the time of the experiment the peptic cells of the

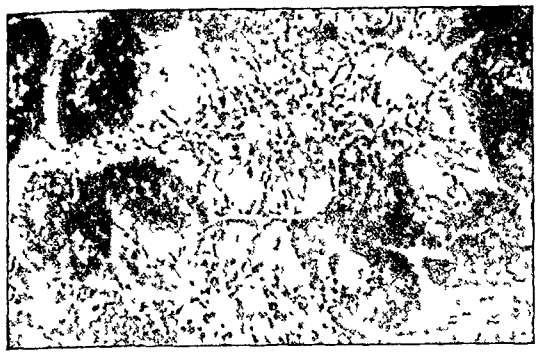


Fig. 3. Corpus. Fed control animal. Peptic cells contain secretory granules near the lumen. Filamentous mitochondria in the basal portions of the cells. Acid cells filled with dark granules. Regaud: Altmann's acid fuchsin. (Oil immersion).

fundus are similar to those in the corpus of the previous animal. The peptic cells of the corpus of this animal contain less secretory granules and more mitochondria. These differences in granule content coincide with the greater digestive activity in this animal. The acid cells are uniformly filled with numerous granules (Fig. 3). Throughout the mucosa the acid cells are similar in character (Fig. 1).

One hour after stimulation with pilocarpine the peptic cells are smaller. There are no secretory granules in the cells except in those in the basal portions of the glands. The mitochondria are scattered irregularly throughout the cytoplasm. The glandular lumina are wider. There is a greater amount of pepsin and acid in the gastric contents. The granules of the acid cells basal to the neck portions of the chief glands are markedly reduced in number, enlarged and stain more faintly so that the unchanged dark neck portions stand in sharp contrast (Fig. 2).

Three hours after the injection of pilocarpine the peptic cells show still fewer granules. There is, however, a small number of large granules in a few cells at the bases of the glands. The mitochondria are short, slender, wavy, more numerous and diffusely distributed throughout the cytoplasm. The pepsin content of the mucosa is markedly decreased; that of the contents is increased. The acid cells basal to the neck portions of the glands contain more granules than in

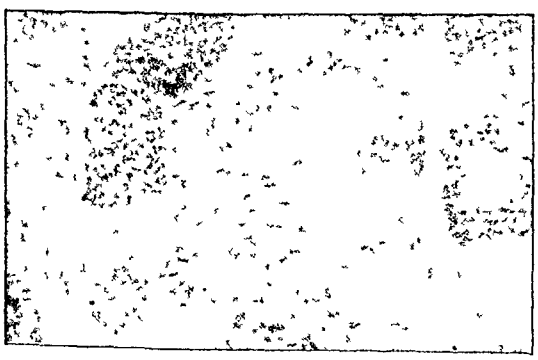


Fig. 4. Corpus. Three hours after injection of pilocarpine. Disappearance of secretory granules from peptic cells. Short mitochondria distributed throughout the cells. Acid cells contain fewer granules. Clear areas around the nucleus. Regaud: Altmann's acid fuchsin. (Oil immersion).

the preceding animal. Clear areas appear in the cytoplasm around the nucleus (Fig. 4). Short, thick rods appear in the central portions of the cells. The acid cells in the most basal portions of the glands are still pale.

Six hours after the injection of pilocarpine the peptic cells are larger. Granules of different sizes appear at the free borders of the cells. This is especially prominent in the basal portions of the mucosa. The mitochondria are longer and for the most part, arranged parallel to the long axis of the cells. They are slender, wavy and often extend from the basal portions of the cells to the region of reappearance of the secretory granules. Many of the mitochondria have eliptical and round bulbous ends. A larger number of acid cells now have central clear peri-nuclear zones. The granules are accumulated concentrically around the border of the cell (Fig. 5). The rods in the central portions of the cells are more elongated and often curved.

Sixteen hours after the injection of pilocarpine secretory granules again fill the superficial portions of the peptic cells The acid and peptic cells closely re-

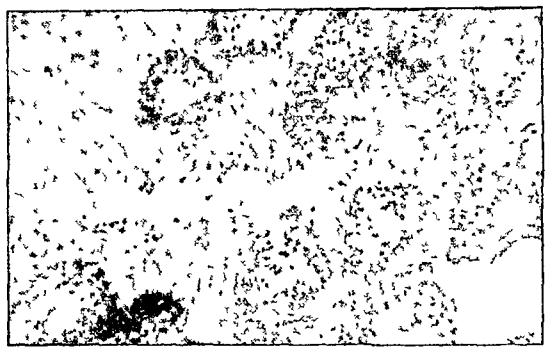


Fig. 5. Corpus. Six hours after injection of pilocarpine. Reappearance of secretory granules at the free borders of the peptic cells. Mitochondria are long, filamentous, and have bulbous extremities. Larger, clear perinuclear spaces in the acid cells. Regaud: Altmann's acid fuchsin. (Oil immersion).

semble those of the fed control animal. The pepsin content of the mucosa rises.

Simultaneously the Golgi apparatus in the peptic cells undergoes distinct variations in form and distribution. In the starved control animal where the peptic cells are packed with secretory granules the Golgi apparatus consists of a small, compact network or small fragments situated near the nucleus on the side toward the lumen. In the fed control where the secretory granules occupy only the superficial portions of the cells the apparatus forms a looser network which is lightly impregnated with osmic acid. It is situated between the nucleus and the free border and extends partially into the region of the secretory granules. With the disappearance of the granules the apparatus becomes more extensive and more darkly impregnated and is situated near the free border of the cell. This process progresses before any secretory granules have reappeared. During the elaboration of the secretory granules the apparatus lies wholly within the region of their formation. As the granules increase in number the apparatus becomes very extensive and appears to consist of impregnated fragments

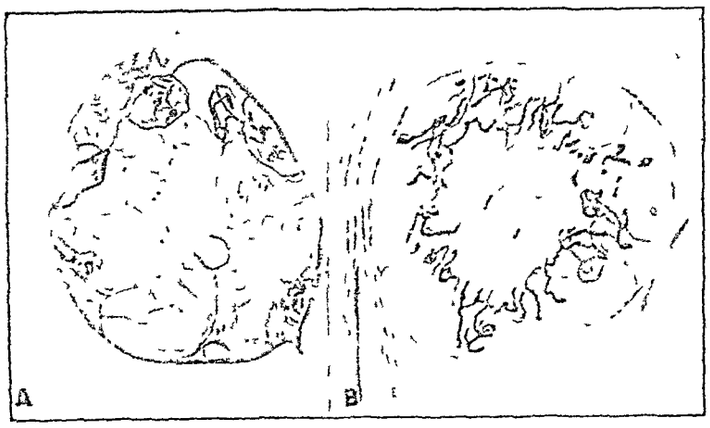


Fig. 6. Antrum. Fed control animal. A. Cells contain large amounts of mucus. Bouin: Heidenhain's hematoxylin-Best's carmine. (Camera lucida drawing from oil immersion). B. Golgi apparatus lightly impregnated; forms a loose network of fine strands. Champy; Kolatchev modified by Nassonov. (Camera lucida drawing from oil immersion).

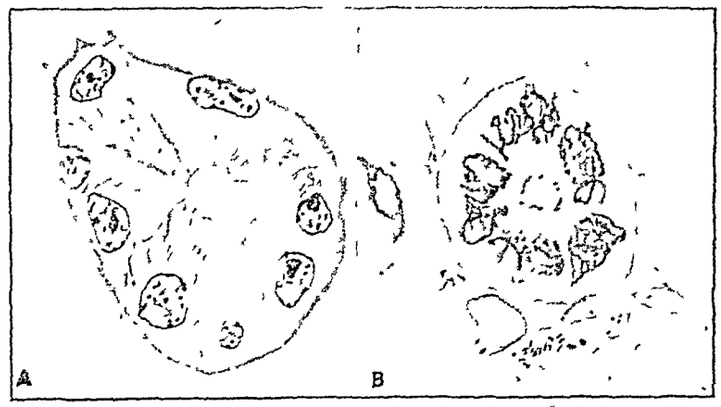


Fig. 7. Antrum. One hour after injection of pilocarpine. A. Mucus markedly decreased. Bouin; Heidenhain's hematoxylin—Best's carmine. (Camera lucida drawing from oil immersion). B. Golgi apparatus forms large, dense, heavily impregnated network. Champy: Kolatchev modified by Nassonov. (Camera lucida drawing from oil immersion).

interspersed among the secretory granules. This state exists until the cells are entirely filled when the apparatus reverts to the resting phase described in the fasting control animal.

A Golgi apparatus has never been clearly demonstrated in the acid cells. Our studies thus far do not permit any definite conclusions.

The action of pilocarpine on the mucus-secreting glands of the antrum is conspicuously depicted in the cytological changes. In the fed control animal the cells contain a large amount of mucus. The Golgi apparatus consists of thin, interlacing strands extending across the entire width of the cells in a zone just above the nucleus (Fig. 6). During all the stages of activity this relationship to the nucleus is maintained. One hour after injection the cells contain only a small amount of mucus near the lumen. The Golgi apparatus is now a dense, large, extensive, heavily impregnated network (Fig. 7). Two hours later the cells already contain more mucus and thereafter continue to store. The Golgi apparatus, however, shows little change until six hours after injection when it decreases in extent and density. In the twelve hour animal the cells are completely filled with mucus. The Golgi apparatus overlies the nucleus and is small and lightly impregnated. It is smaller than the Golgi apparatus in the mucus cells of the fed control animal. The mitochondria do not undergo striking changes.

SUMMARY

A cycle of cyto-physiological changes in the peptic, acid and mucus cells of the gastric mucosa of the rabbit following stimulation by pilocarpine is demonstrated.

SECTION III—*Nutrition*

Vitamin Deficiency in Prescription Diets of Diabetics:†

A Study into the Relationship of Diet Deficiency to Symptomatology as Observed in 85 Diabetics with Previous Dietary Treatment.

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THE physician who has made a careful observation of the dietary habits of his patients, in private practice or the clinic, will have obtained sufficient data to infer that disease may result from diet deficiency as well as from bacteria, parasites or toxins. For instance, conditions such as scurvy, rickets, xerophthalmia or night blindness, pellagra, various forms of undescribed dermatosis as well as certain types of anemia, beriberi, peripheral and other forms of neuritis; disorders of the mouth—such as early decay of the teeth, hyperemic, swollen and tender gums—are improved and to a large extent alleviated by the correction of the diet.

In due time we shall have sufficient evidence for the assumption that various endocrine and other unknown pathological disturbances are the result of diet deficiency. McLester (1) states, "Man's place in future history will depend in no small degree on the food he eats——an animal's life processes may be profoundly disrupted by the omission from its food of any one of a number of substances, each of them ridiculously small in the amount required——. In the future it promises to those races who will take advantage of the newer knowledge of nutrition a larger stature, greater vigor, increased longevity and a higher level of cultural attainment. To a measurable degree, man is now master of his own destiny, where once he was subject only to the grim hand of Fate."

The work at present in the field of vitamins is voluminous, as the material published in the various medical journals throughout the world attest. Several vitamins have been isolated and studied both for their chemical and biological properties. The vitamins that have been isolated chemically have been shown to possess vital nutritional factors which are essential for the human body. In our modern world when people are pressed for time they are liable to omit from their diet, in spite of an abundance of food intake, articles of food containing the essential element: *Vitamins.* This is more apparent in classes of people who "fill up" on one or two kinds of food and omit those which help to make a liberal diet. The consequence to our intricate organism is that the normal replacement and requirement of the vast variety of tissues which help to maintain normal metabolism becomes disrupted resulting in various pathological disturbances. An example of such a disturbance was that of a young man coming to our metabolic clinic who developed symptoms and signs of early scurvy evidenced by bleeding and tender gums from a diet consisting chiefly of meat and macaroni. The condition was alleviated by the correction of the diet. To quote E. V. McCollum: "There are at least 37 individual substances essential for a complete diet. These consist of amino-acids (derived from proteins), dextrose, minerals and vitamins. An adequate supply of all these is absolutely essential for life."

There was a time when a physician concentrated his efforts or skill in the treatment of the patient's ailments without much thought to his nutritional state, too interested in the thought that diseases are generally associated with positive agents such as parasites, toxins, the materies morbi = ignoring diet. Today numerous disease deficiencies are recognized, and many others are constantly being discovered. Perhaps many of the inflammatory conditions of unknown origin may be due to dietary deficiency. As Wilder and Wilbur (2) state, "The tendency has been to get away from the treatment of the disease alone and to consider the general nutritive state of the patient." This view, of course, has widened the field of nutrition and caused nutritional disorders to be more easily recognized.

In order to be better able to treat the nutritive state of the individual much should be known of what constitutes a normal, adequate and optimum diet, and what signs or symptoms are produced by its deficiency. Newburgh (3) states, "The physician must decide whether the condition of the patient requires an increase or a decrease, of any one or several of the dietary constituents so that he may modify the normal diet to meet the new requirements." Perhaps in no other field of medicine has the advance of chemistry been more manifest than in the study of vitamins in our natural food. This study has resulted in a more exact knowledge of the composition of natural foods,

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because vitamins have been isolated and identified as chemical substances. This knowledge has done much to aid us in the prevention of disease and the treatment of the sick. Brown (4) calls vitamins, "exogenous hormones" supplied in the diet while hormones are produced in the body. Hopkins (5) emphasizes the fact that one should not separate the functions of the hormones from those of vitamins too widely to appreciate the extent to which chemical substances control and coordinate events in the animal body by virtue of their specific molecular structure. Together they form a large group of substances of which every one exerts upon physiological events its own indispensable chemical influence. McLester (1) claims the preponderance of evidence indicate that the increased growth achieved by well-considered improvement in the diet is accompanied by general physiologic betterment and definite improvement of the species. Also the hastening of maturity may not be of interest to many people, the postponement of senility through betterment of the diet is an alluring thought to every one. Himsworth and Marshall (6) draw the conclusion from diet observations of diabetics prior to onset of the disease that habitual ingestion of a diet containing a diminished proportion of carbohydrate may cause progressive permanent impairment of sugar tolerance and insulin sensitivity so that diabetes mellitus results in the course of time. Mendel (7) emphasizes that diet in every-day life consists of something more than simple mixtures of the commonly recognized foodstuffs such as milk conspicuously represents. Vegetable products, he claims, in the form of leaves, roots, tubers, buds and fruits enter abundantly into the rations of man and of animals. Although unique nutrient advantages are being ascribed to these foods, our knowledge of what actually happens to them chemically in long reaches of the alimentary tract is woefully limited.

Already the medical literature is being crowded with data describing the therapeutic application of the various vitamin concentrate or their equivalent in the treatment of various pathological conditions or states caused by hypovitaminosis or avitaminosis. Wendt (8) describes vitamin A therapy in goiter; Tarr and McNeile (9) claim deficiency of vitamin B in diet of pregnant and lactating women produced pronounced symptoms. Boulin (10) infers from observation that vitamin B exerts a favorable action in certain cases of diabetes so improving the carbohydrate tolerance that the insulin requirement is reduced. This has inspired many with the thought that vitamin B medication could be a substitute for insulin. Drigalski (11) carried on a series of experiments which disproved such substitution. Junghans (12) describes the process of arresting capillary hemorrhages by parenteral administration of vitamin C (cevitamic acid) in gynecologic cases. Quigley (13) made observations in 2707 persons suffering from various types of tumor. He found that all, more or less, were on deficient diets. The correction of the diet alleviated in a large percentage the unpleasant effects of the concurrent diseases and the patients enjoyed better health. Wendt (14) demonstrated that thyroid influences the vitamin A metabolism. Experiments (15) have shown that deprivation of vitamin D insufficient in degree to cause rickets will however produce hypertrophy and hyperplasia of the parathyroid glands. Gierhake (16) verified the work of Evans and Burr that the absence of vitamin E in the diet is followed by sterility, the addition of the vitamin in the diet resulting in the alleviation of the condition. Kerley (17) observed that children on diets deficient in vitamin B were indifferent, lazy and suspectible to infections such as tuberculosis and common colds. In supplying the essential vitamins to children he advises the natural foods in preference to artificial vitamin preparations.

In view of these facts we decided to make a careful study of the dietary habits of a group of patients coming to the Metabolic Department of the St. Agnes Hospital suffering from symptoms other than diabetes. For this purpose we selected the ones who have been under treatment from 3 weeks to 27 years previous to coming to our department. The total number examined were 85 diabetics. The purpose of course was to find what part vitamins played in the patient's symptoms and signs, and the alleviation of these by supplementing the natural foods in the prescribed proportions containing the essential vitamins. This entailed a study into the food habits. Quality and quantity of food eaten were roughly estimated as "small," "medium," "average serving" or "large helpings"; what foods were not desired because of distaste or idiocyncracy; whether meals were eaten regularly or not. This detailed dietary study involved the period prior to the patient's knowledge of the onset of diabetes. Then we inquired into the dietary treatment during the period of the disease. For clarification we may call the former period as the *pre-diabetic,* the latter as the *diabetic.* In the diabetic period we inquired what foods were prohibited and permitted by their family physician in the course of their treatment. Then we studied the symptomology, its duration as also the diabetic disturbances; insulin therapy, its duration and the total dosage for the day as also the age, weight changes, blood chemistry and complications.

RESULTS OF OBSERVATIONS

In the pre-diabetic period we found that 20 or (23%) of the group did not desire fruits, 49 or (56%) never cared for or gave a thought to drinking milk, 12 or (13%) did not care for vegetables; 15 or (17%) specified particular vegetables they did not desire and ate little vegetable with an effort, 34 or (40%) ate pastry, candy or plain sugar, 39 or (45%) were great bread eaters, 32% were overeaters and all ate their meals irregularly. The age variations were from 11 to 77 years.

Table I is a tabulated list of foods which were denied the patients during their *diabetic period.* To this list we inserted their vitamin contents. We have also found this list to be rich in such mineral elements as calcium, sodium and potassium salts, iron, copper and manganese which play a vital part in the structure and function of the body particularly the bones, teeth, soft tissues, and body fluids. Such elements enter into various bodily functions without any planning on our part and for such reasons we did not insert the mineral contents of the various foods. Patients

who avoided the various foods in the list gave as reasons that they were advised because they contained "sugar," or produced "acid" in the system.

The symbols (18) indicate the vitamin content (18, 19, 21, 21) of the foods:

food, everything else which we eat was "intended" by nature for some other purpose. Vegetables are also rich in minerals and vitamins, many of which were also denied the patient. Cereals which are good sources of vitamin B and G factors, which control skin and

TABLE I

Table of foods denied during diabetic period with their vitamin content

FOODS	VITAMINS A	B	C	E	G
Beans, lima	+	++	.	++	—
Potato, white	+	++	++	.	++
Potato, sweet	+++	++	++	.	.
Peas, dry	+	++	?	++	+
Beans, string	++	++	++	++	.
Carrots	+++	++	++	.	++
Beets, roots	+	+	+	.	+
Cabbage head, cooked	+	++	+	.	++
Rice (polished) white	—	—	—	—	—
Spinach	+++	+	++	.	+++
Lettuce	+ to +++	++	++	++	++
Turnip, white	— to +	++	++	.	++
Broccoli	++	++	+	.	++
Mushrooms	— to +	++	.	.	++
Squash, Hubbard	++	.	.	.	.
Corn, white	+	++	—	++	+
"Dried" or "leafy" vegetables	+ to +++	+ to +++	+ to +++	— to ++	— to ++
Milk, whole	+++	+	+ Variable	++	+++
Cereal	—	+++	—	+++	.
Eggs	+++	+ to ++	— ?	.	+++
Bread, whole wheat, (water)	+	+++	?	++	+
Fruits, all kind	+ to +++	+ to +++	+ to +++	.	— to ++
Beef	+	++	— to +	.	++
Pork	— to +	++	—	.	++
Bacon	— to +	+ to ++	?	.	++
Mutton	— to +	++	.	.	+
Liver	++ to +++	++	+	.	+++
Lamb	— to +	++	.	.	+
Oysters	++	++	+	.	++
Clams	++	.	.	.	.
Fish	— to +	++	.	.	— to +++

\+ signifies an appreciable source.
++ signifies good.
+++ signifies excellent.
— signifies no appreciable amounts.
? signifies doubt as to vitamin value.
. signifies evidence lacking or appears insufficient.

Mild, bread and *other foods* are now enriched with vitamin D by irradiation processes or by the addition of concentrates of natural vitamin D; egg yolks, clams, oysters, as also fish liver oils which are rich in vitamin A, contain rich source of vitamin D.

Fruits of all kinds were prohibited in the diabetic treatment. As we know, fruits are one of life's protective foods, being rich in mineral elements and in vitamins; we well know that oranges and lemons are excellent sources of vitamin C, protector against scurvy. Milk, according to Sherman, is the only article of diet whose sole function in nature is to serve as

gastro-intestinal disorders, were also denied of the patients (Table II).

Thirty-one per cent of the patients were prescribed special diabetic preparations as gluten bread, diabetic muffins, etc. Is it a wonder the patients broke their dietary instructions with such artificial and restricted diet? *Typical of such restriction is that of a diabetic patient, aged 67 years, under a doctor's care for diabetes, 3 weeks, who recently came to our Metabolic Clinic with the complaint of extreme weakness, vertigo, and rapid loss of weight. He stated he was denied not* only *milk, fruits* but also water. It was impossible for him to adhere to such a diet and he had to break the

doctor's rules to satisfy his instinctive nutritional desires. All this because the doctor found a trace of sugar in his urine, in spite of the fact his fasting blood sugar was 147 mg./100 c.c. when he first entered our clinic.

The fact that most of our biological results are obtained from animal experiments, aids us in recognizing clinical disorders. It has been proved that vitamins are chemical substances present in minute quantities in natural foods upon which the normal function and development of the body depend, and they are essential to life. Deficiency or absence of food containing vitamin A results in disorders of the epidermis, eye, gastro-intestinal and genito-urinary tracts and lowering of resistance to infection. The conditions are improved or alleviated by supplementing the diet with food containing the vitamin. The value of many of these changes has been substantiated in man by various clinical investigators. The lack of vitamin B produces loss of gastro-intestinal tonicity, loss of weight, weakness and lack of vigor. McCollum (22) is of the opinion that vitamin B is essential for perfect nutrition of the nervous system and should be a part of the diet of patients with ulcers. That a neurotic element is a predisposing factor in the etiology of ulcer is accepted by many gastro-enterologists. Its relationship to beriberi needs no further comment as it is well known. Various investigators have sufficient evidence that many people are lacking in amount of vitamin C or ascorbic acid optimum for health. The lack of this vitamin produces scurvy and fragility of the capillaries. Experimental studies have shown that apical abscess from devitalized tooth may be caused by deficiency of vitamin C. Harris and Ray (23) have shown that infants suffering from manifested scurvy excrete less vitamin C in their urine than do well-nourished infants of the same age on controlled diets low in vitamin C. After cure the scorbutic infant behaved like a normal infant. It is well established that lack of vitamin D produces rickets and, in no small degree, suspectibility to respiratory infections as well as to dental caries. Goldberger and his associates (24) have done extensive research in vitamin G (B_2) deficiency associated with pellagra and possible other skin disorders. The correlation of vitamin E with sterility by Evans (25) have shown encouraging results.

In the following *summary the symptoms* were taken on the initial visit of the patients who were denied the vitamin rich foods in the diabetic period. We tried not to include diabetic symptoms.

Head: Tenderness and pain to touch "all over" head, at times marked; sharp and "achy" pains in frontal, maxillary and ethmoid sinus regions; *headache*, frontal, occipital, temporal and parietal areas.

Ear-Nose-Throat: Difficulty in breathing; frequent "sore-throat"; "lump" in neck; nose bleed easily; impairment of hearing in both ears to complete deafness in one ear; "head colds," "running nose"; pain in ear-canal as also back of ear, occasional "ear discharge"; excess wax; dryness of skin of ears with scaliness.

Mouth: Receding, tender, swollen gums; bleed easily; looseness of teeth, multiple cavities; soreness of tongue.

Eyes: "Blood shot"; itchy, scaly and swollen lids; visional disturbances in his distance, near or both; blurring and double vision; partial to complete blindness in one or other eye; "shooting" pains occasionally in eyeballs; overflow of tear fluid; slight "bulging" of eye-balls.

Respiratory: Shortness of breath; frequent "chest colds" accompanied by coughing spells; chest pains, radiating, spasmodic and sharp along rib border accompanied by numerous "itching" blisters; sometimes dull ache between shoulders.

Gastro-intestinal: Indigestion, "heart-burn," "sour" stomach, "bloated" feeling in stomach, belching, (excessive gas formation); pain in gall bladder region; constipation, attacks of looseness of stools; sharp pains, spasmodic in times on sides of abdomen, occasional nausea and vomiting; rectal discharge, itch and sometimes sharp pain during bowel movement. Appetite not good, a few could go all day with only two or three cups of plain coffee or tea.

Genito-Urinary: Sharp pains over kidney areas radiating toward bladder; frequent, burning, painful urination; increased desire to urinate; blood in urine, passing of "stones" or "sand."

Extremities: Cold, numb and tingling sensations; mild to marked weakness in legs; "cramps" in muscles of legs and feet; difficult walking; swollen ankles; pus discharge from "ulcer in callous of foot" and from "ulcer of leg in region of ankle," accompanied by slight pain; varicose veins; sharp pains radiating from hip to knee and foot and also from shoulder to hands; sharp pains in one or both shoulder joints following any physical effort; twitching with marked tremor of arms, hands, legs and feet with "loss of muscle power" at infrequent intervals; general ache; painful joints of hands with swelling, aggravated by movements; "cold" hands and feet.

Skin: Dry; itch (general and local); scaly; pallor; red (small) spots distributed over legs and hips; "bruises" easily following any blow, resulting in bluish discoloration. Marked bluish discoloration of skin of feet; yellowish tinge to skin of face and body; easily blanching of feet and hands; marked itch between toes and "soles" of feet; large "blister" on big toe.

Neurological: Depressed; irritable; weakness—mild to extreme; "crying spells"; "suicidal intention"; insomnia; "dizzy spells"; easily fatigue; mental disturbances; paralysis on one side of body; fainting spells.

Cardio-vascular: Shortness of breath; palpitation, "heart misses a beat"; heart "pain"; body feels "bloated" or "swollen."

Gyn: Pelvic pain; scanty menses; irregular menstruation; still birth, miscarriage, bloody vaginal discharge; "lump" in breasts.

Of this group 36 or (42%) of the patients were taking insulin and 49 or (56%) of the patients were not.

SUMMARY OF OUR OBSERVATIONS

1. All the patients in the group suffered from symptoms other than diabetes. The disturbances involved the gastro-intestinal, genito-urinary, gynecological and cardiovascular systems as well as the visual field and oral, neurological, skin, joints and endocrine glands. Forty-two or (48.2%) of the patients were

obese; 5.4% suffered from gangrene; 3.5% from malignancy.

2. All the diabetics in our series were still ignorant of the true nature of their condition—a factor in the causation of increased diabetic complications and mortality.

3. All the diabetics were on restricted diets.

4. None of the patients in our group adhered to their prescribed diets.

5. The substitution of artificial foods such as gluten bread, diabetic muffins and the like "diabetic food" for some of the vitamin-rich natural foods are still advocated by many of the physicians.

6. Avitaminosis and hypovitaminosis was found in everyone of the patients in our series. These disturbances were not the result of one vitamin, but of several, as amply evidenced by the patient's dietary history, symptoms, and physical disturbances.

7. Many physicians adjust insulin dosage to the carbohydrate allowance only, disregarding proteins, fats, vitamins and other elements of diet.

8. Forty-two per cent of the diabetics were on insulin and fifty-eight per cent were not.

9. Many physicians advocate insulin first, when blood sugar is slightly elevated without complications, in preference to a basal or maintenance diet, when diet alone could reduce the blood sugar.

10. There was a marked correlation in vitamin-deficiency diets to rise in incidence of diabetes, diabetic complications or concurrent diseases.

11. There was no correlation in over-eating to rise in incidence of diabetes or concurrent diseases.

These observations inspired us to determine the effect of correcting the diet of these patients. Burnett (26) explains the cause of the development of disease deficiencies as the failure of normal nutrient substances to unite with the protoplasm of the cells to maintain them in a healthy state; such a disorder often manifesting itself in diametrically opposite structural changes in the tissues. He describes cases to substantiate his theory—pellagra in which there is a general atrophy of the cells; and in vitamin A deficiency in animals and patients with pernicious anemia in which there is a hyperplasia of abnormal cells in the bone marrow. Smith (27) is of the opinion that the various pathological conditions are simply the result of disordered nutrition through lack of certain essentials or unfavorable proportions of substances which depend upon one another for their utilizations or some metabolic disturbance which prevents the assimilation and utilization, of the available materials. Salter (28) emphasizes two fundamental concepts for which accessory food-substance play in metabolic processes. (1) Discovery of pro-vitamin's material in foodstuffs which may be transformed by the animal recipient into vitamins. (2) To those who care for the sick is the idea of "conditioned" vitamin deficiency occurring with a normal diet. In the face of abnormal conditions, it is no longer considered safe to place too great a trust in normal, average figures for vitamins requirement.

To insure proper utilization of the food, we examined all patients carefully to determine whether they were suffering from any physical disturbances which would interfere with the proper metabolism of the food. If such a disturbance was found, we tried to correct it so as to prevent what Castle (29) termed "conditioned deficiency" because a normal intake of vitamin is insufficient due to the condition of the patient. In correcting these diet deficiencies we advised natural foods in preference to artificial concentrates or special vitamin preparations. The report of the Council on Pharmacy and Chemistry (30) states, "It has apparently been forgotten that no necessity has been found for administering preparations containing complex combinations for effective maintenance of health when a well balanced diet is taken"—"when a specific vitamin in its natural state is administered utilization in the normal body is adjusted according to a nicely regulated mechanism."

Another factor which must be considered is the cost and the availability of such special preparations as vitamin concentrates or "diabetic foods." The costs of especially prepared diabetic foods or concentrates are too expensive for common use by persons of somewhat limited means. "Artificial substitutes for ordinary foods are not to be favored; it is much better for the diabetic patient to learn how to plan his diet with foods in common use and readily available" (31). Goddard, Sandifur and Beatty (32) found that special proprietary, diabetic and reducing foods varied in percentage composition. They found that some furnished no calories but merely bulk; others contained less carbohydrate or less available fat than the corresponding ordinary foods, still others contained as much potential sugar as ordinary food. Shohl (33) demonstrated that rats on normal diet retained three times as much calcium and five times as much phosphorous as those on rachitogemic diets.

In supplying natural food we stressed a variety of vegetables, fruits, meat, cheese and milk. No special diabetic preparations were advocated. All the patients were placed upon a high carbohydrate diet between 100-180 grams per day, proteins 60-80 grams, fats 80-120 grams, and we advocated vitamin-rich foods so that the patient would receive the various vitamins to alleviate any signs or symptoms which apparently were caused by their deficiency. In view of the fact that none of the ordinary foods with the exception of butter and egg-yolk contain any appreciable amount of vitamin D, we found that the main source would be milk vitaminized by irradiation or the milk of cows which had been fed irradiated yeast. Wherever possible we advocated sufficient exposure to sunlight in addition to other hygienic measures as exercise, daily walks, care of the eyes, mouth, bowels and fluid intake. In prescribing the diets to the clinic patients, we had to consider the cost, advocating adequate amounts of foods which were marketed at a price the patients could afford. These diets were prepared by our chief dietitian, Miss Joyce O'Neill.

Foods (34) tabulated below were advocated in any quantity the patient desired without consideration of

carbohydrate content. In the table below is inserted their vitamin (18, 20) content.

TABLE II

FOODS	A	B	C	G
Asparagus	Variable	++	+++ ?	+++ ?
Celery	— to +	++	++	·
Cucumber	— to +	+	++ ?	·
Cranberries	+	—	++	—
Green Beets	+	+	+	+
Green dandelion	++	++	+	++
Lemons	+	++	+++	++
Lettuce	+ to ++	++	++	++
Limes	—	·	++	·
Mushrooms	— to +	++	—	++
Okra	++	++	·	·
Radishes	— to +	++	++	·
Rhubarb	·	·	+	·
Spinach	+++	+	++	+++

These foods which were found to be rich in vitamins and minerals, but poor in carbohydrate, served to satisfy the appetite. In reasonable amounts in the diet these foods gave bulk to the intestinal residues and helped to relieve constipation. We have found that the patients allowed such foods showed no increase of blood sugar but rather as improvement in their physical condition. The insulin patients were given insulin within 15-20 minutes after meals and not before (35).

The effects of the correction of the diet deficiency were noted by the changes in the symptoms and signs, blood chemistry, insulin dosages, weight and the patient's mental aspect. The duration of the dietary treatment varied from 10 days to 14 months.

RESULTS OF NATURAL FOOD VITAMIN DIET

1. All the patients in the group showed better adherence to the natural food diet.

2. All showed improvement and reduction in their symptomatology of the gynecological, cardiovascular, gastro-intestinal, neurological and genito-urinary systems as also of the joints, oral, nose, throat, and visual fields. Patients with partial or complete deafness, blindness due to cataract, retinitis, optic atrophy or neuritis showed no improvement of the affected part but a diminution of concurrent disturbances and better metabolic control. Such disturbances as sciatica, neuritis, generalized ache or pain, fatigue, weakness, headache, constipation, insomnia, irritability, mental disturbance, tingling, numbness, epigastric discomfort, muscle pain, toxic erythema, acute dermatitis, perforating ulcer of foot and obesity were almost completely alleviated, an improvement resulting in better metabolic equilibrium. Three cases of dermatitis gangrenosa healed without complications.

3. Of three patients of the group who suffered from kidney "colic," two of them after passing numerous "stones or concretions" periodically for 3-4 months showed no more pain, renal or bladder disturbances. The remaining one passed no "stones" but showed relief of "pain" within ten (10) days to the extent of discarding a kidney belt that she had worn for the past four and one-half years.

4. Sixty per cent (60%) of the insulin group were able to discontinue insulin and maintain normal blood sugars. Of the remaining 40 per cent taking insulin half were able to reduce their insulin dosage, though of the other half, the insulin dosage was increased. Of the remaining group (49) who entered our department and who had never been on insulin therapy, 1.6% were given insulin in order to maintain blood sugar optimum for their age.

5. There was less fluctuation of blood sugar in the great majority.

6. All the members in the group took on a more pleasant outlook toward life.

7. Whether the vitamins were supplied in sufficient quantity or not the fact remains that the patients in the group showed marked metabolic improvement on the natural food vitamin diet.

CONCLUSIONS

1. Physicians should interest themselves more in the science of nutrition so as to be better able to detect and treat any diet deficiency.

2. We strongly advocate a more detailed study of the patient's diet history as well as of the symptomatology.

3. The diabetic's diet should consist of natural foods, rich in the essential vitamins and other elements, since such diet will more often result in greater adherence by the patient to his instructions. The following advantages will be obtained:

(1) Better co-operation of patient with doctor,
(2) Less complications, symptoms or physical disturbances,
(3) Less insulin,
(4) Better metabolic equilibrium,
(5) Better outlook upon life,
(6) Prolongation of the span of usefulness,
(7) Greater resistance to infection,
(8) Avoidance of avitaminosis and hypovitaminosis,
(9) More energy.

4. In trying to alleviate physical disturbances due to vitamin deficiency we advocate the administration of natural foods containing the essential elements. Perhaps vitamins depend upon each other for their normal effect within the body in the same manner as the endocrine glands.

5. Diets consisting of a variety of natural foods such as vegetables, fruits, milk and its products, meat and cereals in the prescribed proportions with hygienic measures as sunshine, fresh air and exercise, will result in little need to worry for vitamin deficiency in diabetes.

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Vitamin B Complex Therapy in Chronic Arthritis*

By

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AN atonic bowel associated with chronic arthritis has been found by several clinicians. These clinicians differ somewhat in their remedy. Whereas Fletcher and Graham (1) and Gatewood, et al (2) recommend vitamin B along with restricted carbohydrates as a means to bring about a normal bowel, Pemberton and Pierce (3) on the other hand have been able to return the bowel to a normal contour with the aid of low carbohydrate—low calorie diets which were obviously not very rich in vitamin B. Haft (4) has suggested that any chronic disease may cause the same intestinal abnormalities that are found in chronic arthritis. This thought suggests that treatment of the chronic disease itself should correct the bowel abnormality.

Most research workers have shown that diets deficient in vitamin B cause an atonic bowel. McCarrison (5) fed monkeys food which was first autoclaved and a ballooning of the large bowel occurred. Fletcher (6) could demonstrate atrophy and metaplastic changes in the mucous membrane of the rat's colon by means of a diet high in carbohydrate and low in vitamin B_1. He was able to demonstrate atony of the colon in the rat by diets low in vitamin B. Elsom (7) showed that loss of tone and motility of the gastro-intestinal tract could be brought about in human beings by the administration of diets deficient in vitamin B. McCollum (8) believed that the neurotic element caused by the deficiency of vitamin B in the average American diet was a predisposing element in the etiology of ulcer.

A careful study of the systemic history of the chronic arthritic, omitting the symptoms confined to the joints, shows a marked similarity to that which may be induced by diets deficient in vitamin B.

STRIKING SIMILARITY OF SYMPTOMS CAUSED BY DIETS DEFICIENT IN VITAMIN B COMPLEX AND SYSTEMIC SYMPTOMS IN CHRONIC ARTHRITIS

Chronic Arthritis

1. Digestive disturbances
2. Lack of vigor
3. Disturbance of carbohydrate metabolism
4. Weakness
5. Poor appetite
6. Lowered metabolism

Deficient Vitamin B Diet

1. Digestive disturbances
2. Lack of vigor
3. Impairment of tissue respiration
4. Weakness
5. Poor appetite
6. Glandular dysfunction.

The following findings were obtained in a study of the gastro-intestinal history of 118 patients having chronic arthritis. 105 of this group had atrophic arthritis and 13 had hypertrophic arthritis. Gas, constipation, and anorexia were symptoms present in almost the entire group of 118 patients. Occasional diarrhea, heartburn and epigastric pain were present in a few cases. The gastro-intestinal symptoms were associated in most cases with a systemic complaint of weakness or apathy. Duodenal ulcer symptoms corroborated by the finding of a deformed duodenal cap were noted in four patients in the atrophic arthritic series.** Barium enema studies were made on 24 patients of the atrophic group and the most common abnormality noted was spasticity and not atony of the

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**Since this paper was written two more cases of duodenal ulcer associated with chronic arthritis have been encountered.

colon. In fact, the former was found in 79% and the latter in only 4.1% of the 24 patients.

Are the diets of these arthritic patients deficient in the B complex? Hall and Myers (9) found a deficient or borderline deficient general vitamin diet in 50% of the cases of infectious arthritis, 42.5% of the atrophic arthritics, and in 26.7% of the hypertrophic cases. The non-arthritic control group showed a general vitamin deficiency of 33.3%. Brownson and Steinberg (10) found that whereas the average fruit and vegetable intake of the nonarthritic was two and one-third cups per day, the arthritic ate one and one-half cups of fruits and vegetables per day. With this small difference between the arthritic and the nonarthritic, one could hardly surmise that a lack of vitamin B intake was an etiological factor in chronic arthritis. This, however, does not imply that the vitamin B requirement is not greater in the arthritic than the nonarthritic.

The effect of vitamin B on the gastro-intestinal symptomatology was studied in the series of 118 cases of chronic arthritis. The vast majority had the atrophic type of chronic arthritis. 108 patients were given "Vitamin B Complex" in doses of 4 c.c. to 12 c.c. daily. The usual dose was 4 c.c. twice daily. Ten patients received one cake of brewer's yeast daily. Three patients were given 30 c.c. of a live strain of brewer's yeast which was alternated with the "Vitamin B Complex" preparation with practically identical effects. These preparations were successful in alleviating the gastro-intestinal symptoms in over 95% of the cases. Of the nineteen patients in this study who did not have any gastro-intestinal upsets, a mild diarrhea was occasioned in only one case. The cessation of administration of the vitamin B preparations resulted in the return of symptoms in about 50% of the cases. One to three weeks were required to obtain the beneficial effects of the vitamin preparations. All of the cases preferred the palatability of the "Vitamin B Complex" to the other vitamin products.

Further studies were made to determine any incompatibility between vitamin B complex and two other vitamins: A and D. This group included 20 cases of chronic arthritis with marked gastro-intestinal symptoms of gas and constipation. This group included 13 cases of atrophic arthritis, 3 cases of mixed arthritis with the atrophic factor predominating, 2 cases of Marie-Strumpel arthritis, and two cases of hypertrophic arthritis. Vitamin B complex in doses of 8 c.c. to 12 c.c. daily was given to thirteen cases of this group in periods varying from three months to twelve months with complete cessation of the untoward gastro-intestinal symptoms. At the end of this varying period, massive doses of vitamin D, 250,000 to 750,000 units were given daily for periods varying from two to six weeks in ten of the preceding cases with no change in the already improved status of the gastro-intestinal symptomatology. Two cases that had received improvement with the vitamin B complex were also given 18,600 units of vitamin A and 2700 units of vitamin D daily for another three months with no change in the already attained intestinal improvement. In another case the liquid vitamin B complex preparation was replaced with a capsular form and doses of 18,600 units of vitamin A, 2700 units of vitamin D, and 135 Sherman units of B_1 and 30 Sherman units of B_2 were given daily without any change in the improvement attained with the vitamin B complex preparation. Four patients received massive doses of vitamin D (250,000 to 750,000 units) daily at the same time that the vitamin B complex was started in periods varying from two to three months, with the same beneficial pharmacological effect on the gastro-intestinal tract. Three patients received capsules of 18,600 units of A, 2700 units of D, 135 Sherman units of B_1 and 30 Sherman units of B_2 daily without any initial period of the vitamin B complex with identical beneficial gastro-intestinal symptomatology.

COMMENT

The present trend in thought that vitamin B complex increased the tone of the atonic bowel needs modification. This study indicates that vitamin B complex aids in restoring an abnormal bowel tone to a normal status; the vitamin B complex possesses pharmacological value in restoring this tone whether the bowel be atonic or hypertonic. This is an entirely new concept as to its value. The discovery of four cases of duodenal ulcer in four cases of chronic arthritis along with the suggested apparent increased demand for vitamin B complex in the chronic arthritic opens up another possible attack upon the unknown etiology of peptic ulcer.

CONCLUSIONS

1. Spasticity of the colon is commonly associated with chronic atrophic and hypertrophic arthritis.
2. There is no vitamin B deficiency which accounts for the gastro-intestinal symptomatology present in the cases of chronic arthritis reported in this paper.
3. There probably is an increased demand for vitamin B complex in the chronic arthritic.
4. Four cases of duodenal ulcer are reported in a relatively small number of cases of chronic arthritis.
5. There is no pharmacological incompatibility amongst vitamins A, B, or D as regards the gastro-intestinal effect in the group reported in this paper.
6. In a study of 118 cases of chronic arthritis of which 99 had gastro-intestinal symptoms, it was found that the vitamin B complex is of adjunct value in the treatment of chronic arthritis.

The author takes this opportunity to thank Dr. E. A. Sharp, Director Department of Experimental Medicine, Parke, Davis & Co., for his assistance in supplying the vitamin preparations for this study.

He also expresses his gratitude to Dr. L. R. Lingman, Director Department of Radiology, Rochester Central hospital for the radiographic interpretations.

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SECTION IV—*Roentgenology*

The Roentgen Diagnosis of Acute Intestinal Obstruction

By

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IT is surprising that so objective and reliable a criterion as the roentgen method for the diagnosis of acute intestinal obstruction, should not have attained the universal recognition among clinicians that the procedure deserves.

As far back as 1911, Schwarz (1) of Vienna, described four cases in which by the oral administration of bismuth, he established the diagnosis of obstruction of the small intestine. He demonstrated the following points: First, dilatation of the loops of small intestine, approaching the colon in size; second, exaggeration of Kerkrings folds; third, fluid levels capped by gas in the dilated small bowel in the erect position; fourth, delay in the motor function of the small intestine.

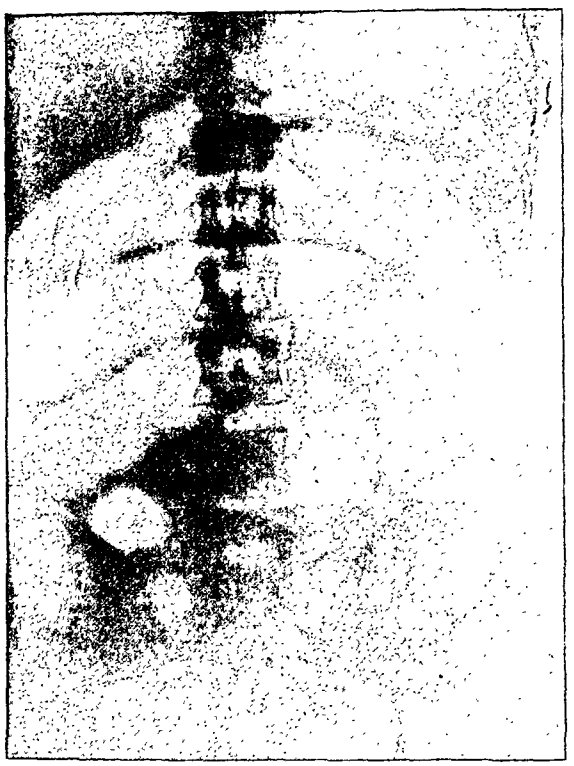


Fig. 1. Note the marked dilatation of the coils of small intestine and the arrangement like a spiral spring. No fluid levels are noted because the film was taken in the prone position.

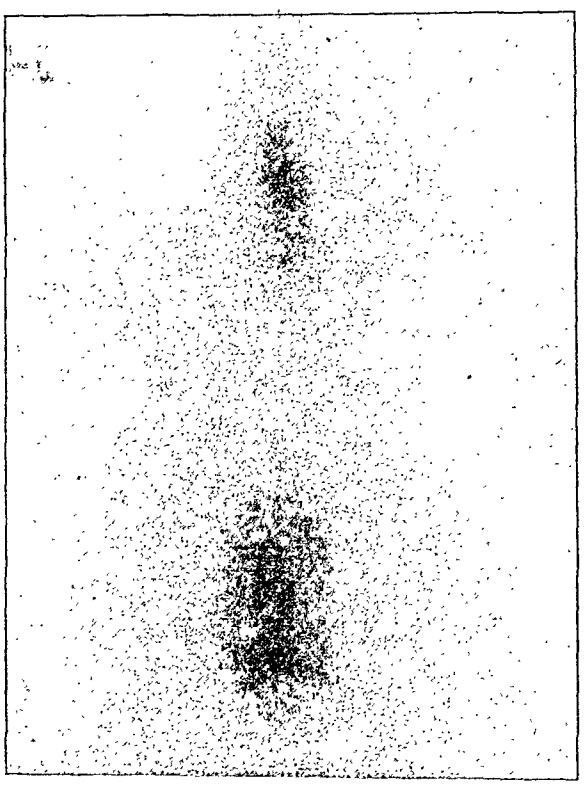


Fig. 2. Note the numerous fluid levels throughout the abdomen, surmounted by gas. This is the classical appearance in acute obstruction of the small intestine when the film is taken in the erect position.

These classical findings were corroborated in 1913 by the famous Stierlin (2) who made one valuable additional observation. In a child four years old who developed evidence of intestinal obstruction one week

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Submitted August 24, 1936.



Fig. 3. Note the marked dilatation of the loops of small intestine. The folds of Kerkring are prominently shown.



Fig. 5. Another example of acute intestinal obstruction showing gas capped fluid levels.

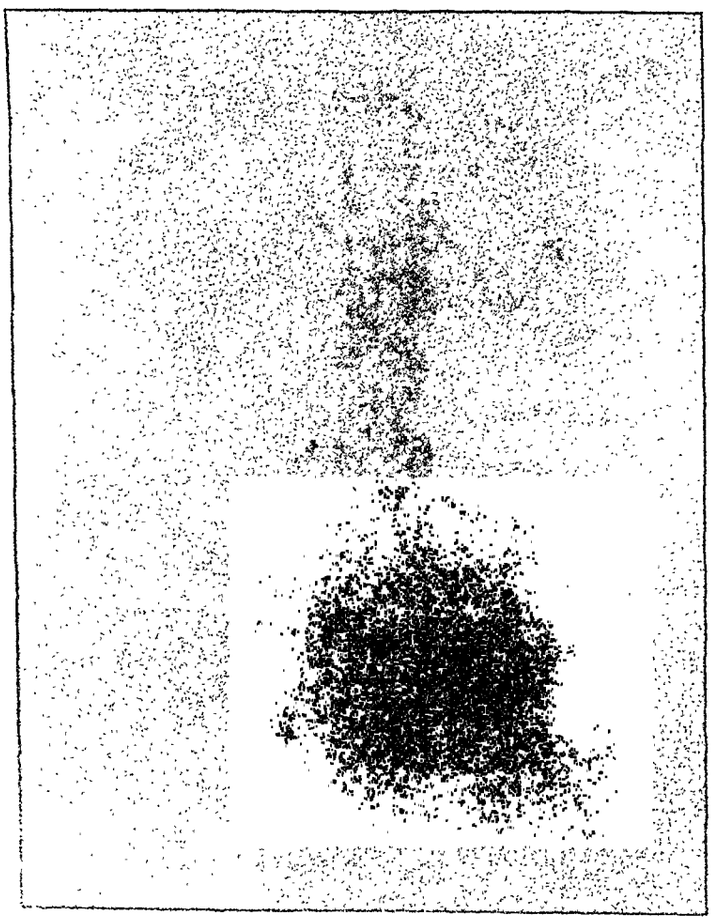


Fig. 4. Marked dilatation of the small intestine with unusual prominence of the folds of Kerkring.

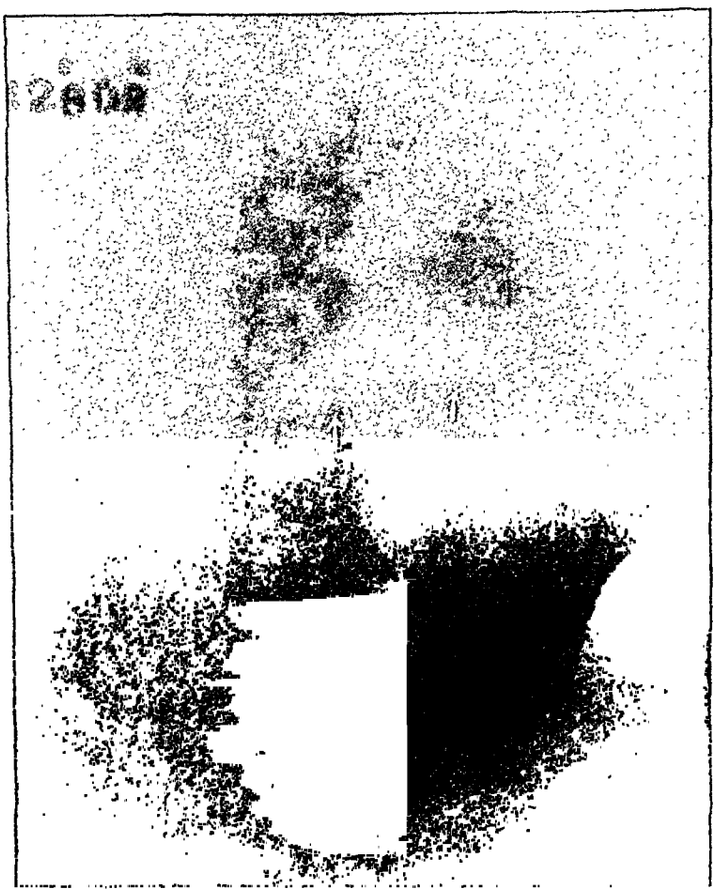


Fig. 6. This roentgenogram taken in the erect position exhibits distention of the small bowel, fluid levels surmounted by air caps, and prominence of Kerkring's folds.



Fig. 7. Obstructive Malignant Lesion of the Sigmoid. The flat plate shows a complete arrest of the gas in the colon at side of new growth.

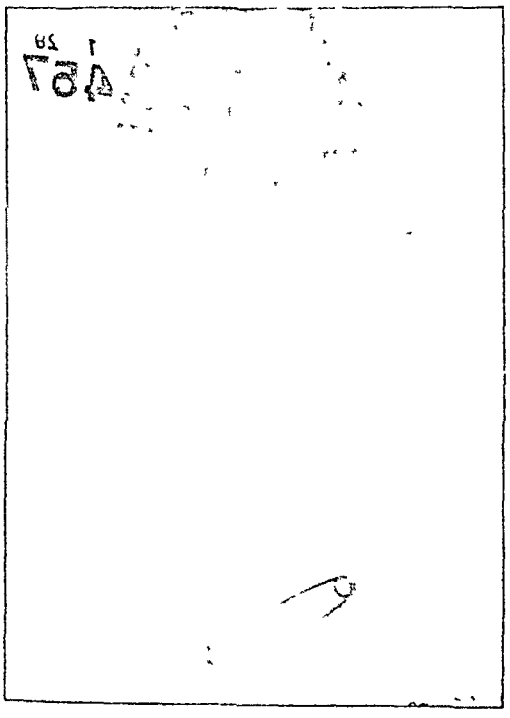


Fig 8. Congenital Atresia of the Transverse Colon in a Newborn Infant (verified at autopsy). Note the unusual prominence of the gas distended loops of small intestine. Film taken in the erect position.

after an appendectomy the roentgenogram showed the characteristic evidence of marked dilatation of the loops of small intestine, although no bismuth was administered by mouth. The child died and at autopsy adhesions and abscess formation were found to have caused the intestinal obstruction.

Much water has pased under the bridge since these two memorable and fundamental contributions were made to the diagnosis of obstruction of the small intestine and a fairly large literature has arisen since then, emphasizing the great significance of the method.

Notable among these are the contributions of Novack (3), Czyhlarz and Selka (4), and particularly that of Assmann (5) who in 1913 also described the dilatation of the small intestine with fluid levels surmounted by gas bubbles as seen roentgenologically even prior to the administration of bismuth by mouth.

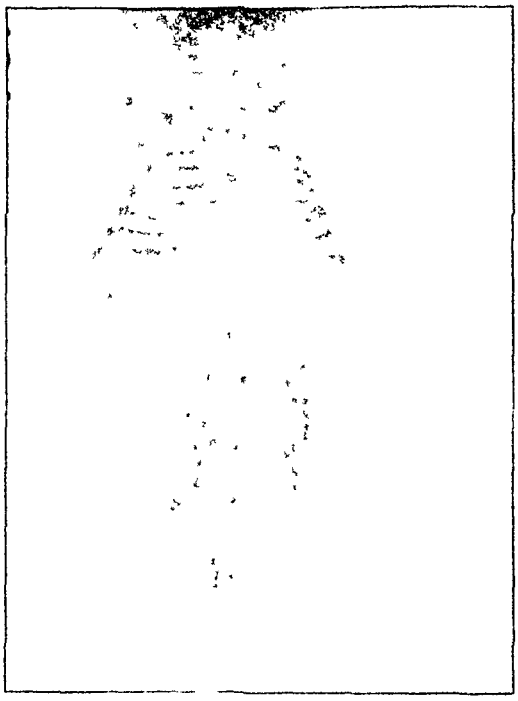


Fig. 9. (Same Case as Fig. 8). Appearance after barium enema. Complete arrest of the barium at the mid portion of the transverse colon.

It is this ability to roentgenologically recognize the presence of obstruction of the small intestine, without the administration of an opaque medium by mouth, that was later emphasized by Marcuse (6), Case (7, 8), Kloiber (9), Ginzburg (10), Wangensteen (11), Rendich (12), and others Kloiber showed that a characteristic roentgen picture could be obtained within three hours after the onset of clinical symptoms eventuating in intestinal obstruction.

In this country, Case particularly did pioneer work in establishing the validity of the roentgen diagnosis of acute intestinal obstruction.

The rapidity with which characteristic roentgen evidence appears after the onset of obstruction, is of course of enormous importance, because of the rapidly increasing mortality with every hour of delay in surgical intervention.

It is interesting therefore to note that in experimentally produced simple obstruction in the dog Ochsner (13), showed that gas distention of the small bowel occurred as early as one hour later and fluid levels in three hours. Hibbard, Swenson and Levin (14), were able to show gas shadows as early as one and one-half hours after ligation of the superior mesenteric artery in dogs, and the development of fluid levels in four hours. It is this ability to roentgenologically demonstrate evidence of intestinal obstruction, long before the clinical picture has become clear, that constitutes the life saving value of this simple diagnostic procedure. The film should preferably be taken in the erect posture when possible, to show fluid levels, although films in the prone and lateral positions are also of considerable diagnostic value.

Not only is the administration of barium by mouth unnecessary, but it may in some cases do considerable harm. Particularly noteworthy is the observation of Smithies (15) who described four cases in which an acute intestinal obstruction was converted into a perforation after the ingestion of barium.

Reflex ileus may infrequently produce the roentgen appearance of acute obstruction of the small intestine. Among such possible causes, may be ureteral colic and acute pancreatitis or a twisted ovarian cyst. Assmann many years ago (1913) described the intestinal contraction of lead colic as capable of producing fluid levels in the roentgenogram. Also he described fluid levels in tetany and in tuberculous peritonitis without actual ileus. The differentiation between dynamic and adynamic ileus by the roentgen method is in my opinion impossible. Clinically such differentiation may be possible by auscultation. The 'ominously silent abdomen' of Deaver may indicate the presence of an ileus of adynamic origin.

A small amount of gas may sometimes be normally present in the small intestine of the adult, and even fluid levels scattered throughout the alimentary tract may be noted after catharsis (Rendich).

The classical roentgen picture, however, rarely gives rise to any doubt. Where the evidence is of a borderline nature, examination at frequent intervals may clear up the difficulty.

Interpreted in the light of the clinical history, the flat film, taken prone, laterally and particularly in the erect position, furnishes objective evidence of enormous importance as a life saving measure in establishing the early diagnosis of acute intestinal obstruction.

The following are reproductions of films chosen to exhibit the roentgen characteristics in operatively proven cases, which justified the diagnosis of acute intestinal obstruction.

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SECTION V—*Therapeutics*

What Drug Best Kills Hookworms?

By

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IN the interests of the individual and the community, treatment of hookworm infection in man should aim at complete deworming (1). Those who hold that fewer than twenty-five (or a hundred) worms are harmless to the individual, do so on scant evidence (Lane, 1932). In public health, the inference (Molloy, 1933) that a community of 618 souls should view with a quiet mind the fouling of their precincts by 1,383,350 hookworm eggs *every day* is unacceptable.

THE TESTS

Worm loads are commonly estimated by egg counts. This is doubly unwise. First, the rate of ovipositing

*Editorial Editor, "Helminthology," Tropical Diseases Bulletin, London, England.

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varies with species, age and number of worms; with diet, drink and drugs taken by the host and probably with the presence of other worms. Second, egg counts are no true measure of worm loads, for different techniques using the same stirred stool may give quite different totals.

The most erratic in my hands has been Stoll's, hence my suggestion that all using it should check it in their own hands. For this, Ahmann and Bristol (1933) report two essentials—a training period of fifty slides; the counting and averaging of at least four slides from each suspension. Little of the world's helmintholo-gical literature escapes collection by the Bureau of Hygiene and Tropical Diseases. I call to mind no paper reporting that this care has been taken in converting egg numbers into worm loads. As judged by controls, the most accurate egg-counting technique in my hands is D.C.F.F. (2). It has been decried by those who have altered it in essentials, transferred the odium to the original, and let the matter rest there. On present evidence, it is the most accurate means of determining the egg-content of feces; diagnostic techniques must then be graded by it. So tested, the best of them is D.C.F. It will disclose a single normally ovipositing *Ancylostoma duodenale* or *Necator americanus*. By its use Kendrick (1934) found the life-span of *A. duodenale* longer by one to three years and of *N. americanus* by four years than shown by Stoll's method. Only then, by tests for deworming can anthelminthic drugs adequately be graded. This is now a rapid matter, for the area needing examination in a herded D.C.F. preparation is about 9 sq.mm., and with a twelve-tube centrifuge, four men can make and examine these preparations at the rate of 250,000 yearly.

THE ANTHELMINTHIC DRUGS

Since hookworms rarely kill directly there is no justification for putting efficiency of anthelminthics before their safety.

Thymol. Its optimum dosage is grs. 60. Its crystals, if packed, coalesce into a solid unabsorbed mass unless particulation is effected, as by grinding it fine with at least an equal part of, say, milk sugar or sodium bicarbonate. It is on particulation that its efficiency depends. Thus, Washburn and Payne in Trinidad had, after two optimum treatments, a deworming rate of 12.6 from plain and one of 49.1 from particulated thymol. British Guiana and Ceylon confirmed this; and from the extent of films examined, all these figures must have been close to accuracy. Giles (1890) held that pouring an alcoholic solution of thymol into some eight times its volume of water and shaking vigorously gave a particulated and potent suspension; the physical result is a very fine floccular particulation, though when not so shaken, the tiny globules which first form, coalesce, and by evaporation give rise to large floating plates. Its potency after such precipitation still awaits proper testing. Caius and Mhaskar (1919) showed that after particulation by grinding, no thymol was found in the feces or in the worms passed, nor was most of the loss accounted for by known derivatives in the urine. On analogy with quinine and emetine, I suggest that something formed from thymol by the host is the true vermicide. At least, fear of dangerous absorption induced by alcohol seems ill-founded, as Bozzolo too felt. The postmortem appearances of all cases I have been able to collect (1932) differ, except for two brothers dosed together, and reappearing after an absence in the woods to die of acute gastro-enteritis. If all died from thymol this is perhaps unique. Howard (1919) reported a million cases in the United States with no death when instructions had been carried out, and Ashford (3) 1,600,000 in Porto Rico with no death. My own 60,000 administrations without anxiety are relatively unimportant. These facts are insufficiently weighed by those who dub my conclusions as old-fashioned and reactionary. There is still that prejudice for the new which struck Paul of Tarsus in the Athenians some 1900 years ago; there is also that preference for proof among careful physicians with patients' lives in their hands. It makes for safety that thymol is apt to produce "drunkenness" in a dose well below the fatal one. (Foot Note)

Beta naphthol. The minimum lethal dose is 20 grains (Milne, 1933), lower ones are inefficient. Suppression after passage of smoky urine is a marked feature.

Oil of chenopodium. The active and lethal principle, ascaridole, varies from 33 to 98 per cent, the doses fatal to man and worm are close together, and the size of drops, by which it has been constantly measured, vary from 18 to 70 to the c.c. It is commonly given without knowledge and report of its ascaridole content. It seems never to have been checked by tests for deworming when the ascaridole content was known, so that after hundreds of thousands of administrations its real worth is unknown. It has killed a number of subjects, but perhaps not an adult man in a dose of 0.8 c.c. of ascaridole. It may cause permanent deafness.

Carbon tetrachloride. The minimum lethal dose, habitually exceeded and relatively inert, is 1.5 c.c. (Bais, 1924). It produces liver necrosis greatest round the hepatic vein, regeneration taking place from cells surviving about the portal vein; but ankylostomiasis itself may produce degeneration about the portal vein (Ashford and King, 1907) and presumably defeat regeneration. Excess of blood guanidine is a grave risk, added to by calcium deficiency, and it is among persons so suffering that hookworm campaigns are usually undertaken (Ashford, 1933). Instinctive calcium hunger is perhaps shown by Dr. J. W. Lindsay (3), for, in Paraguay, poor country children often scrape off and eat the whitewash from dispensary walls, which may have to be rewhitened several times a week. Concommitant ascaris infection is a marked danger. Yet the drug is often given in "herd fashion" without microscopic confirmation of hookworm infection or exclusion of any dangerous factor. With Ashford's experience of 1,600,000 doses of thymol with no death, compare nineteen deaths in the same number of doses of carbon tetrachloride in Egypt (Tomb and Helmy, 1933) and the ambiguous statement of Khalil (Hassan and Salah, 1935) that seven or eight cases of "poisoning" are reported yearly by the Parquet in Egypt.

Chenopodium and Carbon Tetrachloride. Tests are few, and the oil's ascaridole content unstated in all.

Foot Note: To avoid the poisonous effects of thymol administered in effective anthelmintic dose, 30 to 60 grains, we have exhibited always after the patient has been on fat-free diet for a minimum of 36 hours prior to the taking of the drug and keeping fat—as cream, butter, etc.—out of the diet for twenty-four hours after the drug has been taken. Black coffee prevents circulatory weakness. A saline purge is given six hours after the last dose of drug. *Editor.*

Soper (1924) with respective doses of 0.6 and 1.8 c.c. had a seeming deworming rate of 35 per cent to Willis's technique, but further treatment showed that it had been only 10%. Maplestone and Mukerji (1929) with respective doses of 1 and 3 c.c. had a deworming rate of 26.3 to D.C.F.

Ascaridole and carbon tetrachloride. With respective doses of 0.75 and 1 c.c. (Pessôa, 1924), the real cure rate was unknown, but two of forty-eight treated became so ill that thirteen refused a second controlling treatment.

Ecuador experience. Soper (1935) wrote regarding the suspected recrudescence of yellow fever in South America, that after many postmortem "viscerotomies" on these cases, pathologists disagreed on the significance of the lesions; but against yellow fever were the facts that none occurred in the cities, immunity tests on children were negative, and clinical histories were inconclusive; yet all save one had received anthelminthic treatment of an unstated kind. The pertinent experience of J. W. Lindsay in Paraguay is that after treatment by oil of chenopodium or carbon tetrachloride or both in standard doses according to age, given by native orderlies not always under professional control there have been deaths in children, and in adults, ruined health with enlarged liver and jaundice (3). At present grave responsibility rests on all using or advising this treatment.

Tetrachlorethylene. No death has yet been reported though Kendrick (1929) was very anxious in one of 15 administrations when 3 c.c. were given to a man of 10 stone. Lambert wrote (1933) "I report . . . . . over 46,000 treatments with tetrachlorethylene without death and without untoward symptoms." His dosage was 15 to 60 minims, but the results of treatment were unstated, presumably unknown. Maplestone and Mukerji (1929) had to D.C.F., 15 per cent of deworming in forty patients with a dose of 3 c.c. Garrison (1934) had, to a brine floatation method, 93 per cent of cures among institutional children with a dose of 3 c.c. for a child of ten, but the inadequacy of the best of these methods had been noted above.

Tetrachlorethylene and oil of chenopodium. With respective doses of 3 and 1 c.c. Maplestone and Mukerji (1929) had a 28.2 per cent deworming rate to D.C.F., and when tetrachlorethylene was increased to 4 c.c. (1933) one of 62 per cent. The ascaridole content was noted in neither. Without reporting controls, they advise that the drugs should be given shaken up in 2 oz. of magnesium sulphate solution to produce subdivision and enhance potency. Presumably the latter fails, for Darling, Barber and Hacker (1920) had better results with plain than emulsified chenopodium oil; and as to the former, in my observation tetrachlorethylene precipitates visibly in ten seconds, and almost completely in sixty seconds after this shaking.

Hexylresorcinol. Molloy's dosage was 1.05 gram for all over eleven years old; two treatments gave to Stoll's technique a deworming rate of 19.4 per cent. It must have been less, for Maplestone and Mukerji (1929) had eight apparent cures to Stoll's method after tetrachlorethylene treatment, but D.C.F. showed that only one was dewormed. The drug causes great erosion of the mucosa, which encapsulation happily shifts out of a mother's sight unless a perverse child chews a capsule.

CONCLUSIONS

For individual, community, or medical man investigating anthelminthics, complete deworming is the only stable aim. The deadline of anthelmintics is urged against this aim. But, before reaching the dangerous stage, thymol and tetrachlorethylene, like alcohol, give warning which makes for safety. Though it was probably these timely symptoms which led to the disuse of thymol, they are now being used to recommend tetrachlorethylene. The evidence for the safety of thymol is more solid than for any other drugs, so the objection to deworming by it is poorly based; its efficiency depends upon particulation, but the effect of the finest particulation has never been measured. Tetrachlorethylene merits controlled tests on a proper scale. The cheapness of beta-naphthol is no balance to its risks. Oil of chenopodium must not be given without knowledge of its ascaridole content, seeing how near together are the optimum and minimum lethal doses; its production of deafness is not negligible. Carbon tetrachloride is liable to be either highly extrolled or dropped when it kills; to look before giving it for the factors known to make for deadliness is constantly neglected; with oil of chenopodium it lies under grave suspicion of ruining health and causing death in South America with simulation of yellow fever. Hexylresorcinol "also ran," not having fulfilled the expectations of its introducers.

There is urgent need for the carrying through by experienced medical men of controlled comparative tests on an adequate scale to determine on the only stable basis—deworming—what anthelmintic is the safest and most effective in the expulsion of hookworm. Such stable knowledge is long overdue.

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The Spastic Colon Diet

By

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THE spastic colon demands special dietetic consideration. One is for a smooth diet. Alvarez has particularly described and emphasized this indication. The smoothness in this connection means generally low content of cellulose in the food stuffs. Another special indication has reference to the susceptibility of food stuffs to putrefactive bacterial action; which susceptibility, as well as the absorption of putrefactive products from the intestine, is favored by the abnormal functioning of the colon. These two indications, *viz,* for smoothness and for inferior susceptibility to putrefactive bacterial action, particularly guide in the selection of food stuffs for the spastic colon diet.

For supplying the protein ration in this diet, *milk* is the preferred food. Milk is free from indigestible residue and is protected to a certain extent from the action of putrefactive bacteria by its dissolved carbohydrate, lactose, which is readily fermented by the lactic acid bacteria. (Acidification makes for inhibition of putrefaction). By milk is meant not only milk, but also modification of milk and preparations of milk and of its separated constitutents.

Milk may be mixed with water, cereal preparations, strained fresh fruit juices and strained decoctions of vegetables. Milk and barley water, strained milk and oatmeal gruel (made with cooked oatmeal porridge which is cooked a second time in the milk and strained), milk and cooked cream of wheat and milk with the cream of wheat cooked in it, are examples of cereal mixtures.

A serviceable mixture with fresh fruit juice is made with strained orange juice, the latter being sufficient in quantity to curdle the milk in fine flakes on agitation.

Useful mixtures with strained cooked vegetables are the pureed milk soups, as cream of celery, tomato, corn, carrot, etc.

Modifications of milk produced by fermentation used in this diet are those made with lactic acid producing bacteria and yeast—the sour milks and koumyss.

Predigested milk — peptonized and pancreatized — serves a useful purpose in some instances.

Of the *cheeses,* cream and cottage cheese are the most suitable, although rennin-made cheese, as American Cheddar, Parmesan and Edam cheese may sometimes be used if properly comminuted and made smooth, as in cheese sauce baked with macaroni.

Eggs, although belonging in the distinctly putrefactive class of food stuffs, have a place in this diet because of their freedom from insoluble residue and their easy digestibility.

Cereals, selected with due regard to their cellulose content, have an important place in the dietetic management of spastic colitis. Their use in combination with milk has been referred to. Cream of wheat and rice deprived of its hulls, are comparatively smooth when boiled. White bread twenty-four or more hours old, especially if toasted, can be used by many patients. Oatmeal in the form of the strained gruel is generally acceptable, if the straining is effective.

The *sugars,* as they occur naturally in fruits and milk, are acceptable, also to a certain extent, honey; cane sugar is generally to be avoided.

Of the *fat foods,* olive oil, butter and cream have the highest rating. Some patients tolerate butter more readily than they do cream, which seems, of the two, to be the more often productive of digestive disturbances. Olive oil taken late in the evening, the patient lying on the right side for a short time immediately following its ingestion in order to facilitate its passage from the stomach into the intestine, may be useful as a laxative.

Among the acceptable *fruits* in this diet the first place would seem to belong to the banana (1). The edible portion of the fully ripe banana contains (2): Water, 75.6%; Protein, 1.3%; Fat, 0.6%; Carbohydrate, (Dextrose, 4.5, Levulose, 3.5, Sucrose, 11.9, Starch, 1.2) 21.1%; Ash, 0.8%; Crude fiber, 0.6%.

In respect to their mineral content, bananas are "relatively rich in phosphorus, magnesium, potassium and sodium, and also contain copper and manganese." They are particularly rich in their content of vitamin A; and they contain fair quantities of vitamins B, C and G. They are exceptionally well protected from bacterial invasion while in the market by their thick capsule. These qualities of the banana, *viz,* its high nutritive value (the average sized banana supplies 100 calories), its easy digestibility and its low content of insoluble residue, especially recommend it for the spastic colon diet. Its "roughage," moreover, which is comparatively smooth"—Bogart refers to its "soft texture,"—can act as a gentle laxative without producing much irritation to the spastic colon.

But the banana must be fully ripe for this diet. Ripeness in indicated by the dark spots which appear on its capsule; also it must be prepared in a special manner. After being peeled, the "fuzz" must be scraped off. The fruit must be masticated thoroughly to a pulp, or, better, mashed before being eaten, in order to preclude the possibility of lumps being carried from the stomach and small intestine into the colon.

The banana may be eaten plain as above described, or in mixtures. A serviceable mixture is made with cream cheese, in the proportions of two parts of the banana to one of the cream cheese, or in other proportions. Six ounces of this two-to-one mixture supply protein, 14 grams; fat, 16 grams; carbohydrate, 26 grams, and have a fuel value of 310 calories. In-

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stead of cream cheese, cottage cheese may be used in this mixture if a lower caloric value is desired.

The banana pulp also may be mixed with milk, cream, or strained fresh orange, grape-fruit or pine-apple juice; or the fruit juice may be added to the banana and cream cheese mixture.

In addition to banana, among fruit food stuffs in this diet, strained juice of fresh orange, grapefruit and pineapple, pure, or mixed with water, are acceptable. The pulp of baked apple, or even stewed apple, may be well borne by some patients.

The vegetables allowed in the management of the spastic colon must be "smooth," which means, in the case of the leafy and stalky vegetables, the green seeds and seed pods, the gourds, bulbs and roots, that they require straining after they have been cooked.

Of the *salad vegetables*, raw tomato, which has had the skin and seeds removed, generally is acceptable.

Water should be given in good quantity, but not in excessive quantity.

Table salt should be given in ordinary rations, but not in excess.

The *beverages* containing caffein generally are contraindicated.

Spices are forbidden.

Animal flesh usually should be avoided, but to certain patients, some of it may be allowed. The flesh foods containing small amounts of fibrous tissue are to be preferred, as for example the breast of chicken. Also, fishes, those with low fat content which are of easy digestibility, are to be preferred. There is a place in this diet, although only an occasional one, for clear meat broths as stimulants to appetites and digestion.

All food in this diet should be taken neither very hot nor very cold.

The following diet lists are constructed in accordance with the facts and principles above mentioned. They lend themselves easily to modifications to suit particular needs.

SPASTIC COLON—DIET I

(Protein, 85 gms. Fat, 110 gms. Carbohydrate, 215 gms. Calories, 2200).

Breakfast

Moist cooked cream of wheat, 120 gms. (4 oz.).
Toasted white bread, 30 gms. (1 oz.).
Egg, soft boiled or poached, 1.
Butter, 15 gms. (½ oz.).

At 10 a. m. (or with breakfast)

Milk, 180 gms. (6 oz.), mixed with strained orange juice, 60 gms. (2 oz.); or milk or junket, 240 gms. (8 oz.).

Dinner

Strained milk-vegetable soup, *viz:* cream of celery, carrot, tomato, potato, green pea, onion, oyster plant or spinach, 240 gms. (8 oz.).

Banana, ripe, with "fuzz" scraped off, mashed, 120 gms. (4 oz.), mixed with cream cheese, 60 gms. (2 oz.).

Toasted white bread, 30 gms. (2 oz.).
Moist cooked rice, 120 gms. (4 oz.).
Butter, 15 gms. (½ oz.).

At 4 p. m. The same as at 10 a. m.

Supper

Banana and cream cheese mixture as at dinner.

Strained boiled squash, carrot, spinach, string beans, green peas or lima beans, 180 gms. (6 oz.).

Milk, or milk soup as at dinner, or junket, or buttermilk, 240 gms. (8 oz.).

Tomato, raw, with skin and seeds removed, 130 gms. (4 oz.).

Toasted white bread, 30 gms. (1 oz.).

Butter, 15 gms. (½ oz.).

SPASTIC COLON—DIET II

(Protein, 68 gms. Fat, 77 gms. Carbohydrate, 166 gms. Calories, 1600).

Breakfast

Banana mixture, as in *Spastic Colon—Diet I*, 180 gms. (6 oz.).

Milk and oatmeal gruel, made with oatmeal porridge cooked a second time in four times its quantity of milk, and strained, 240 gms. (8 oz.).

At 10 a. m.

Milk and orange mixture, as in *Spastic Colon—Diet I*, or milk or junket, 240 gms. (8 oz.).

Dinner

Banana and cream cheese mixture as at breakfast.

Milk, 120 gms. (4 oz.), mixed with cream, 60 gms. (2 oz.), and barley water, 60 gms. (2 oz.).

At 4 p. m.

The same as at 10 a. m.

Supper

Banana and cream cheese mixture as at breakfast.

Milk soup, as in *Spastic Colon—Diet I*, 240 gms. (8 oz.).

By special order, moist cream of wheat, 180 gms. (6 oz.), may be added to dinner; or an extra feeding of any of the milk combinations may be given at night.

SPASTIC COLON—DIET III

(Protein, 55 gms. Fat, 75 gms. Carbohydrate, 120 gms. Calories, 1380).

At 7 a. m.

Milk or junket or buttermilk, 240 gms. (8 oz.).

At 9 a. m.

Milk and orange juice mixture as in *Spastic Colon—Diet I*, 240 gms. (8 oz.).

At 11 a. m.

Strained milk and oatmeal gruel, as in *Spastic Colon—Diet II*, 240 gms. (8 oz).)

At 1 p. m.

The same as at 9 a. m.

At 3 p. m.

The milk, cream and barley water mixture, as in *Spastic Colon—Diet II*, 240 gms. (8 oz.).

At 5 p. m.

The same as at 9 a. m.

At 7 p. m.

Milk soup, as in *Spastic Colon—Diet I*, 240 gms. (8 oz.).

At 9 p. m.

The same as at 11 a. m.

Substitution of one preparation for another in the above list may be allowed by special order.

An extra feeding of any of the above preparations may be allowed during the night by special order.

Spastic Colon—Diet I is intended for the average ambulant patient. It has a caloric value sufficient for a life of moderate activity. If the patient is confined to bed, the fuel ration may require reduction. If increased physical activity calls for a larger fuel ration, that can be supplied by addition of cereals, butter, olive oil or cream.

If the patient is able to manage a more liberal diet, a small portion of chicken or fish may be substituted for part of the cream cheese; or the number of eggs may be increased. A small portion of clear broth, made with chicken, beef, mutton or clam may be allowed in certain instances.

Substitutions for the purpose of increasing variety and catering to individual tastes and idiosyncrasies easily can be made in accordance with the principles above specified.

An ounce of olive oil, given at night, when the stomach is empty, may have a good laxative effect.

Spastic Colon—Diet II and *Spastic Colon—Diet III* are intended for the more severely ill and bed-fast patients. In most instances it may be well to begin treatment with one of these or a similar diet, and enlarge the diet as the patient's condition improves.

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SECTION VII—*Surgery of the Lower Colon and Rectum*

Anal Fissure, Anal Spasm and Anal Stenosis

By

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NARROWING of the anal circumference, produced either by muscle spasm, or fibrosis, the result of a lesion of the anal canal, is a condition frequently encountered. Fissure of the anus, anal spasm, and stenosis, although different lesions, are dealt with together in this presentation because their symptomatology is esentially similar and the treatment to be outlined is applicable to all three conditions.

In order to understand the rationale upon which treatment of these lesions is based, it becomes necessary to review the anatomy of the anal canal, especially in the light of more recent knowledge, together with a consideration of the clinical picture produced by anal fissure, anal spasm and anal stenosis.

ANATOMY OF THE ANAL CANAL CONCERNED IN STUDY

The rectum at a point approximately one and a half inches in front of the tip of the coccyx, that is, at the level of the apex of the prostate in the male, and at the apex of the perineal body in the female, bends abruptly backwards, pierces the rectal layer of pelvic fascia, and becomes the anal canal. The anal canal is a narrow slit-like passage possessing in normal people a fair degree of "comfortable" elasticity and distensibility, to the extent that bulky formed stools or the lubricated index finger may be passed without discomfiture to the subject. It is approximately two inches in length in its posterior half and approximately an inch in length in its anterior half. Its walls, when at rest, lie in coaptation. The viscus is directed backwards and downwards from the end of the rectum through the pelvic floor, to open on the exterior as the anus. The anal canal is totally destitute of peritoneum, but is clothed and supported by a prolongation of the rectal layer of the pelvic fascia which it pierces. The muscles which closely surround the anal canal and ano-rectum (together with their nerve supply) are the major factors entering into this presentation and will have to be considered in detail. The musculature of the ano-rectum is considered in this study along with that of the anal canal, and therefore one is here concerned with the terminal two inches (approximate distance of ano-rectum posteriorly) of the alimentary canal.

The anal canal is surrounded by its muscles, the external and internal sphincters and levatores ani, which form its immediate boundaries in both sexes. Laterally there are the ischio-rectal fossa; an important relation, since it is across this fossa from the posterior aspect of the perianal region that the nerves run to supply the anal musculature. Posteriorly one finds the ano-coccygeal body and coccyx. In the male the membranous part of the urethra and the bulb of the urethra are in front of the canal, but on account of the backward inclination of the gut, are separated from it by a mass of fibro-elastic tissue, corresponding to the perineal body of the female. Anteriorly at the top of the anal canal in close relation to the membranous urethra lies the base of the prostate. In the female the anal canal is separated from the vagina anteriorly by a pyramidal fibrous, fatty and muscular mass, the perineal body. The anal canal is lined by squamous epithelium continuous with the skin of the integument, and not by mucous membrane as is sometimes described. The transition to columnar epithelium occurs above the dentate or pectinate line, i.e., above the level of the crypts of Morgagni. The dentate or pectinate line marks the embryologic junction of the proctodeal membrane, where fusion occurred between the proctodeum and hind gut. Extending up from the crypts or pockets of Morgagni are longitudinal folds of mucous membrane, the columns of Morgagni. The crypts of Morgagni are crowned by small papillae, the anal papillae, which may become hypertrophied, and in some instances, become true polypi. The white line of Hilton, referred to in some text books, is not an anatomical entity, but can be seen as a pale circular area, lying below the pectinate line, and actually is the anal intermuscular septum of fascia which separates the subcutaneous part of the external sphincter from the internal sphincter muscle, and lying beneath the skin of the anal canal thus gives a whitish appearance by reflected light.

Musculature of the anal canal and ano-rectum concerned in this study. The basis of conservative treatment in this presentation of anal fissure, anal spasm, and anal fibrosis, is based upon the principle of rest for a fairly prolonged period of time of the muscles of the anal canal and ano-rectum. This follows the axiom of surgical rest, laid down by John Hilton in his Lectures on "Rest and Pain," as long ago as 1860.

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1933 (1). In order to secure this surgical rest by the measures presently to be described, one must consider in detail the anatomy of the musculature of the anal canal and ano-rectum. The Author in securing a prolonged and adequate anaesthesia of this region, has found this objective possible to attain only by observing closely, in his induction technique, the anatomical studies of Milligan and Morgan (2). In 1934 these two workers published their splendid contribution upon the "Surgical Anatomy of the Anal Canal." By following the anatomical landmarks outlined in their paper, the writer has been able, by the technique to be described, in an almost uninterrupted series of cases, to secure very satisfactory results in the treatment by conservative measures of anal fissure and anal stenosis, in cases which hitherto appeared amenable only to radical surgical measures. In the following *resumé* of the anal musculature insofar as it concerns this thesis, the Author in his descriptions has drawn upon the studies and followed the landmarks of Milligan and Morgan (2).

The external sphincter of the anus is divisible into three portions, *i.e.*, it is a trilaminar muscle which together with the puborectalis portion of the levator ani forms a strong muscular cylinder encircling the outer longitudinal muscle of the bowel wall, the internal sphincter ani and below this level the anal canal. In other words the external sphincter of the anus is not the superficial subcutaneous single muscle so often referred to in text books, but is actually a strong muscular cylinder completely encircling the anal canal as high as the ano-rectum, which at its uppermost level joins with a portion of the levator ani to enter into the formation of the ano-rectum. The three components of the sphincter ani externus muscle are: (e) Sphincter ani externus subcutaneous; (2) Sphincter ani externus superficialis; (3) Sphincter ani externus profundus. Fibromuscular septa from the fascia of the longitudinal muscle of the rectum, actually separate and divide off the three portions of the sphincter ani externus. (1) *The sphincter ani externus subcutaneous*, is the most superficial portion of the external sphincter muscle. It is that division of the external sphincter which lies just beneath the skin, and encircles the lowest portion of the anal canal. It is this portion which is often referred to as "the external sphincter," when, actually, it is only its subcutaneous portion and its least important part as far as continence is concerned. It lies in the same plane as the sphincter ani internus, from which it is separated by an annular band of fascia. The sphincter ani externus subcutaneous can be felt just beneath the skin by passing the finger around the anus externally. It may be cut or divided in any direction with impunity. Posteriorly its fibres do not reach the coccyx. It is completely subcutaneous and directly palpable throughout its circumference. (2) *The sphincter ani externus superficialis*, lies above and lateral to the subcutaneous portion of the external sphincter just described. Posteriorly it has an attachment to the coccyx. It lies between the subcutaneous and deep (sphincter ani externus profundus) portions of the external sphincter but on a more lateral plane and surrounds the sphincter ani internus in its lower two-thirds, together with the downward prolongation of the outer longitudinal muscle of the rectum. Anteriorly, its fibres are inserted into the central point of the perineum. (3) The sphincter ani externus profundus, represents the upper and deepest portion of the sphincter ani externus. It is closely fused with the lower part of the puborectalis portion of the levator ani in the posterior half of its circumference. Its lower part is in close contact with the sphincter ani externus superficialis. It surrounds the downward prolongation of the outer longitudinal muscle of the rectum, and the upper part of the sphincter ani internus. The fibres posteriorly are continuous and have no attachment to the coccyx.

The Puborectalis portion of the levator ani guards and enters into the formation of the anorectal ring. It is highly important as regards rectal function and continence. It takes its origin from the back of the symphysis pubis and from the upper layer of the triangular ligament. Its fibres pass downward and backwards around the lower and lateral aspects of the rectum, meeting with fibres from the opposite side behind the anal canal, so forming a powerful loop or girdle, which slings the anorectal junction to the symphysis pubis. None of these fibres reach the coccyx. The lower border of the puborectalis muscle as already mentioned is intimately blended with the sphincter ani externus profundus. Together with this muscle it fuses posteriorly with the downward prolongation of the outer longitudinal muscle of the rectum and is reinforced by the thickened fibres of the inner circular muscle of the rectum, *i.e.*, the sphincter ani internus which it surrounds. The puborectalis lies at the junction of the rectum and anal canal, can be easily identified with the examining finger, and as first pointed out by Milligan and Morgan enters posteriorly into the formation of the important anorectal ring. The anorectal ring in front, therefore, is made up of the deep part of the external sphincter and the outer longitudinal muscle of the rectum, reinforced by the upper fibres of the internal sphincter ani. Anteriorly the puborectalis leaves a U shaped deficiency of the anal canal and does not enter into the formation of the anorectal ring in front. Anteriorly therefore the anal canal is quite short and suspended to the back of the pubic bones by the insertion of the puborectalis. This is an important consideration in the therapy to be outlined presently for anal fissure and anal stenosis. The outer longtitudinal muscle of the rectum takes part in the formation of the anorectal ring. Its fibres posteriorly blend with the puborectalis which lies external to it, and anteriorly with the fibres of the sphincter ani externus profundus.

At the upper end of the anal canal the outer longtitudinal muscle of the rectum becomes fibromuscular, and dips down to ensheath and surround the three divisions of the sphincter ani externus, and has its terminal attachment to the area between the lower border of the sphincter ani internus and the upper border of the subcutaneous part of the external sphincter, i.e., just beneath the skin of the anal canal where a groove can be identified in the living subject, referred to as the anal intermuscular septum.

The sphincter ani internus represents the inner circular muscle coat of the rectum which encircles the whole of the anal canal down to the anal intermuscular septum, i.e., down to the top of the subcutaneous portion of the external sphincter. Its lower border can be felt and identified just below the muco-cutaneous border of the anal canal, about one-fourth or one-half inch from the anal opening. As pointed out by Milligan and Morgan, it does not form a narrow annular band or ring as is so often depicted.

The anorectal ring guards the junction between anal canal and rectum, and is the muscle structure of prime importance guarding continence. The subcutaneous and superficial portions of the external sphincter, part of the internal sphincter, and any of the structures up to this ring, may be cut or sacrificed with impunity, and yet continence will be preserved. Continence is lost with the sacrifice during surgical operations of this important muscle band. The anorectal ring is a composite fibromuscular band composed of: (a) the upper portion of the internal sphincter, (b) the longtitudinal muscle fibres at this level of the rectum, (c) the puborectalis part of the levator ani posteriorly, and (d) the external sphincter ani profundus muscles. Posteriorly the puborectalis enters into the formation of the anorectal ring, but anteriorly it leaves the anal canal to be inserted into the symphysis pubis leaving a U deficiency. Anteriorly the anorectal ring is formed by the internal sphincter, the longtitudinal muscle, and the deep portion of the external sphincter muscle. Anteriorly thorough fusion of the internal and deep external sphincter muscles have occurred to form a composite flat band and identification by palpation is more difficult than posteriorly, because of the presence of the puborectalis in the posterior part of the anorectal ring. The anorectal ring can be easily identified by digital examination of the rectum. It can be recognized by the palpating finger as a circular ridge or shelf between the top of the anal canal and the rectum. Posteriorly this is quite pronounced, because of the inclusion of the puborectalis portion of the levator ani into the musculature of the anorectal ring. Where this inclusion does not occur anteriorly, the anorectal ring is flatter and not so easily recognized by the examining finger. An important consideration in treatment to be shortly outlined is the difference of the levels between the posterior and anterior parts of the anorectal ring. Posteriorly this ring lies at an approximate distance of two inches from the anal opening, roughly the second crease on the volar aspect of the index finger; anteriorly, the distance from the anal opening is approximately one inch, roughly, the first skin crease on the volar aspect of the index finger. This difference of levels is demonstrated in the diagram. In other words the anorectal ring anteriorly lies in a lower plane than the anorectal ring posteriorly. The anorectal ring slopes downwards from the posterior aspect as an inclined plane to the anterior part of the anorectal circumference, and lies at its lowest level at the anterior anorectum. This difference in levels is approximately one inch. This too is an important consideration in operations upon anorectal fistulae; because posteriorly one can sacrifice sphincter muscle with more impunity than one can anteriorly. In the posterior aspect one can cut down on the sphincter muscles to a height of almost two inches in order to lay the fistulous tract open. Anteriorly one very soon reaches the anorectal ring, since it lies at a distance of only one inch from the anal opening. The rectal surgeon has long recognized the danger of incontinence where much sphincter muscle must be sacrificed anteriorly. The anorectal ring is the final and important arbiter as far as continence is concerned. When this is sacrificed in any part of the anal circumference, incontinence is certain to result.

Certain landmarks in the anal and anorectal musculature always can be palpated and recognized. These landmarks have all been described and are enumerated as follows: 1. The subcutaneous part of the external sphincter ani, which lies just beneath the skin at the anal opening and can be felt throughout its circumference; 2. The anal intermuscular septum; 3. The lower border of the internal sphincter ani, felt and recognized just above the groove of the anal inter-

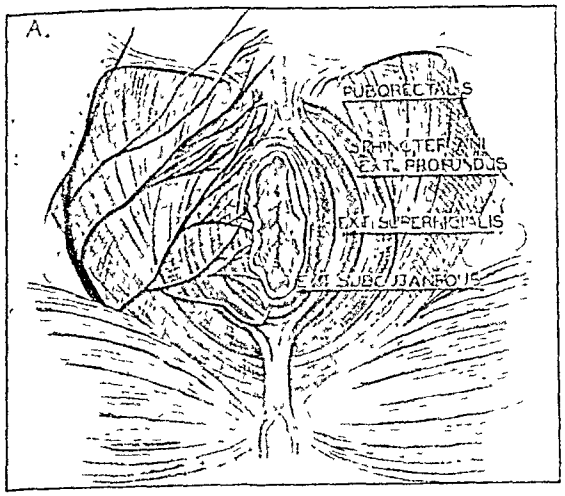


Fig. A. Diagrammatic representation of the musculature of the anal canal and ano-rectum viewed from below. The three portions of the sphincter ani externus muscle are shown in their respective planes. The puborectalis portion of the levator ani muscle can be seen to fuse posteriorly with the deep portion of the sphincter ani externus profundus. Anteriorly the fibres of the puborectalis may be seen leaving the anal canal, and running upwards towards the symphysis. The inferior haemorrhoidal and perineal nerves are shown in position on one side.

muscular septum in the lower part of the anal canal, 4. The anorectal ring; 5. The puborectalis portion of the levatores ani.

NERVE SUPPLY OF THE ANAL MUSCLES AND ANORECTAL RING, CONCERNED IN STUDY

The nerve supply to the muscles of the anal canal and anorectal ring are derived from the third and fourth sacral nerves. The subcutaneous and deep portions of the external sphincter muscle are supplied by the inferior haemorrhoidal nerve which has its origin from the third and fourth sacral nerves. The inferior haemorrhoidal nerve is a comparatively large mixed nerve and one of the three main branches of the pudic nerve which emerges from under cover of the great sacrosciatic ligament. The inferior haemorrhoidal nerve arises in the postero-lateral part of the ischio-rectal fossa and passes forward across the fossa towards the anus. The course that it takes across the ischio-rectal fossa is an important consideration in performing an effective nerve block in the treatment to be outlined. It supplies sensory branches to the skin of the anal canal and peri-anal region and motor branches to the subcutaneous and deep portions of the sphincter ani externus muscle. The superficial portion of the external sphincter muscle is supplied by the large perineal division of the pudic nerve through the fourth sacral. The course of the perineal nerve is like the inferior haemorrhoidal nerve also postero-lateral, but lateral to the latter. The perineal nerve is a mixed nerve, and supplies sensory branches to the skin of the perineum, scrotum or labium majus Some of its sensory fibres anastamose anteriorly with those of the inferior haemorrhoidal nerve to supply the peri-anal skin and that of the anal canal. The sphincter ani internus really the lower continuation of the inner circular muscle of the bowel is supplied with sympathetic nerves in common with the rest of the alimentary tract, but also receives motor nerves through the third and fourth sacral. The levator ani muscle is supplied as well through the third and fourth sacral nerves. Its pelvic portion is supplied by branches from the fourth sacral nerve. The puborectalis is supplied by branches of the internal pudic from the third and fourth sacral nerves. It will be seen from this description that the nerve supply to the muscles of the anus and anorectal ring runs in a forward direction from the postero-lateral perianal aspect, where the nerves lie deep in the subcutaneous fat before they pass inwards to the sphincter muscles. This insures a rich and wholesome motor supply to the posterior and postero-lateral aspects of the muscles which go to make up the anal canal and anorectal musculature. Anteriorly the anal musculature and that of the anorectal ring derive their nerve supply through small terminal filaments of these nerves. As already mentioned the anal musculature is short anteriorly, and in front the puborectalis portion of the levator ani muscle does not join the deep portion of the external sphincter to enter into the formation of the anorectal ring, thus leaving a U shaped deficiency. The puborectalis is fixed to the back of the pubic bones after it leaves the anal canal, acting as a sling to the anterior anorectal ring. The short deficient anal canal and anorectal ring anteriorly devoid of support from the puborectalis, together with its terminal poor nerve supply already pointed out, are factors which render the anal canal quite vulnerable in the anterior part of its circumference. This fact must be recognized in cutting down anterior fistulae, and is further taken advantage of in the conservative treatment to be outlined by the Author for anal fissure, spasm and stenosis.

The skin of the anal canal as far as the pectinate line, is very richly supplied with sensory cerebro-spinal nerves especially from the sensory branches of the inferior haemorrhoidal nerve. Severe pain or burning is therefore a characteristic symptom of any lesion of the anal canal. This by completing the reflex arc produces spasm of the sphincter muscles of the anal canal and anorectal ring. The interpretation, study, and methods of dealing with this clinical picture form the essential substance of this thesis.

CLINICAL STUDY OF THE LESIONS: ANAL FISSURE, ANAL SPASM AND ANAL STENOSIS

Anal fissure may be defined as a break or loss of continuity in the skin of the anal canal, situated as a rule in the posterior aspect of its circumference. It has a strong tendency to become chronic and to resist cure by simple measures. The lesion infrequently occurs in the anterior aspect of the skin of the anal canal. Since the process occurs below the pectinate or dentate line in the anal canal which is lined by squamous epithelium, the lesion therefore is not a one involving the mucosa, as is sometimes erroneously described.

That this break or loss in surface-continuity should most frequently occur in the posterior aspect of the anal canal seems at first difficult to understand. As already pointed out the anal canal is short anteriorly and the anorectal ring lies only a short distance from the anal opening. This renders the anterior circumference of the anal canal quite vulnerable in surgical operations for fistulae, but nevertheless what is present of the anal canal anteriorly is sturdy and formidable. The puborectalis portion of the levator ani further suspends the anal canal to the back of the symphysis pubis, and must be regarded as a protective force. The superficial part of the sphincter ani externus whose fibres fuse in the mid line anteriorly and have a firm insertion into the central point of the perineum, has quite a different arrangement posteriorly. Behind, the fibres decussate to be inserted into the coccyx, forming an angulation as they leave the anal canal to gain this coccygeal insertion. This factor makes for weakness, especially by any distending intra-anal force. The tissues of the perineal body in the female and the fibromuscular body corresponding to this in the male, act as a firm solid support to the anal canal anteriorly and to the area immediately in front of the subcutaneous portion of the external sphincter. This can easily be confirmed by palpating this area. Posteriorly the subcutaneous portion of the external sphincter has no such support by a firm body of fibromuscular tissues, but rather the soft resilient fatty connective tissues between the subcutaneous sphincter and the coccyx. This must be regarded as the important factor rendering the anal canal vulnerable in its posterior circumference, since fissure in ano occurs as a rule posteriorly in the skin of the anal canal overlying the subcutaneous sphincter ani externus. Moreover confirmatory evidence is provided in parous women, in whom anterior fissures are more frequently observed, and who are found to suffer from rupture of the perineal body (rectocele) or thinning out or diastasis of the levatores ani.

The acute fissure manifests itself as a simple loss in surface continuity of the skin of the anal canal, overlying the area of the subcutaneous portion of the external sphincter. There is no induration and very little inflammatory reaction of the surrounding tissues. There is marked spasm of the sphincter muscles of the anal canal up to and including the anorectal ring. Digital examination causes variable degrees of pain and for this reason the anal canal folds in the

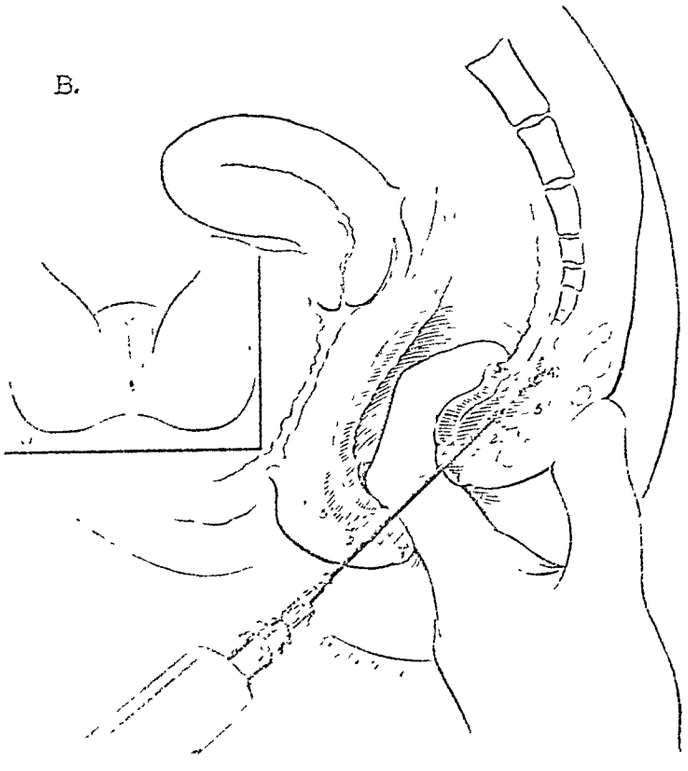


Fig. B. Technique of posterior and postero-lateral anaesthesia. Anaesthetization of the ischio-rectal fossae cannot be demonstrated in this section. The needle is seen traversing the anal and anorectal musculature as high as the anorectal ring. The tip of the finger is hooked around the ridge formed by the anorectal ring, and can be seen to be inserted as far as the second crease on the volar aspect of the digit. (1). Subcutaneous portion of the sphincter ani externus. (2). Superficial portion of the sphincter ani externus. (3). Deep portion of the sphincter ani externus. (4). The puborectalis portion of the levator ani. (5). The anorectal ring, described in text. The sphincter ani internus is shown lying under the finger as a flat and not as an annular muscle.

Fig. B1. The dotted area shows the field of anaesthesia induced by the posterior and postero-lateral technique.

ulcer area, and it takes much patience to retract the anal folds and demonstrate the lesion.

The chronic fissure has induration as its characteristic feature. Its edges are hard and may be in some instances of almost cartilaginous consistency. The anal canal becomes appreciably altered. Whereas in the acute fissure there is spasm of the muscles of the anal canal and anorectal ring, in the chronic fissure there may be actual stenosis of the anal canal. The anal canal is apt to be rigid, fixed and immobile up to and including the anorectal ring. Such is the result of the presence of a chronic, painful irritant, *i.e.*, an insult of long standing. There is an actual fibrosis of the sphincter muscles. This easily may be proved under low spinal anaesthesia, when, in operating upon such patients, there is no relaxation of the sphincter muscles and anal canal. In narrowing of the anal canal whether due to spasm or an actual fibrosis, it becomes impossible for the patient to pass a formed bulky stool of even moderate consistency. Liquifaction of the stool becomes the only alternative in order to effect its passage (3). Fecal impaction in such instances frequently is encountered. Early or late in the course of the ailment, if the acute fissure is not healed with (spontaneous cure rarely occurs) the spasm of the sphincter muscles is replaced by an actual stenosis. One then has a rigid, stenosed, immobile anal canal associated with loss of elasticity and resiliency of its structural components. If the patient be subjected to the painful ordeal of a digital examination, or is subjected to the index finger in the anal canal and the thumb on the perianal area ("bidigital" palpation), the sphincter muscles are felt to be thickened, hypertrophied, non-elastic and firm. The examiner recognizes a "fibrous" feel. This is demonstrable up to and including the anorectal ring, which is thickened and rigid. Because of spasm and hypertrophy, the puborectales are easily identified.

Lawrence Abel, in 1932, described an anatomical entity in the region of the "pecten" in cases of chronic fissure and anal narrowing. He refers to this as the pecten band (4). Abel recognized this band as a circular band of fibrous tissue beneath the pecten of the anal canal, and likened it to a "rubber umbrella" ring. (The "pecten" has been established as that region of the anal canal extending from the anal papillae, *i.e.*, the base of the columns of Morgagni to the "white line" of Hilton, which has already been referred to in this paper). The Author finds that Abel's pecten band corresponds to the anal intermuscular septum, which is the lower circular fibrous portion of the longitudinal muscle of the bowel and which is inserted beneath the skin of the anal canal forming a groove in the normal subject, already referred to as the anal intermuscular septum. The sheath of the longitudinal muscle takes part in the fibrotic process which produces the marked narrowing of the canal. The anal intermuscular septum has become hypertrophied and dense and the Author at present regards this circular fibrous structure as the pecten band referred to in Abel's work. Where anal stenosis has occurred due to a chronic irritant, this circular band normally present, and which can be identified in the normal, as a shallow groove formed by its attachment beneath the skin lining the anal canal in the region between the top of the subcutaneous portion of the external sphincter and the lower border of the sphincter ani internus, has become much accentuated. This the Author regards as the structure referred to by Abel as the pecten band. Although the operation of pectenotomy, *i.e.*, division of this band, will afford some relief; one has to deal with a total fixation of the anal musculature up to and including the anorectal ring. In the Author's opinion pectenotomy although beneficial is therefore regarded as inadequate in dealing with anal stenosis.

Spasm of the musculature of the anal canal and stenosis may result from any irritant or insult in this area. Fissure in ano, while the most frequent cause, is only one of these, and the clinician must deal with those cases presenting spasm or actual stenosis in which no fissure can be demonstrated, and in which other causes are operative. Any factor which produces passive venous congestion in the ring of superior haemorrhoidal veins, which lies quite superficially in the submucosa just above the anorectal ring, (which plexus is concerned in the formation of internal haemorrhoids), will act as an irritant to the anal canal and anal musculature, and result in spasm of the sphincter muscles.

The peculiar arrangement in the lower rectum of a loose redundant mucosa overlying a plexus of superficial veins renders the lower rectum a selective site for the formation of varices. Moreover the portal veins (and the large tributaries) which drain the superior haemorrhoidal area are without valves, and very feeble support is afforded the superior haemorrhoidal plexus by the loose redundant mucosa. With the exception of a slight anastomosis on the surface of the rectum, the portal system practically is a closed circuit, where gravity and physiological stasis especially after meals are constantly at work favouring stasis. It may thus be seen that a dilated state in these veins is easily arrived at, and that the formation of internal haemorrhoids (varices) or anal spasm and anal stenosis may singularly or together be manifestations of a state of passive congestion in the haemorrhoidal veins.

Passive congestion in the haemorrhoidal area may result from numerous systemic causes with the secondary development of anal spasm or stenosis, consequent upon systemic disturbances, *e.g.*, portal obstruction in cirrhosis of the liver, abdominal or pelvic tumors, pregnancy, uterine displacements, pelvic inflammatory disease and prostatism (5). Once spasm has become

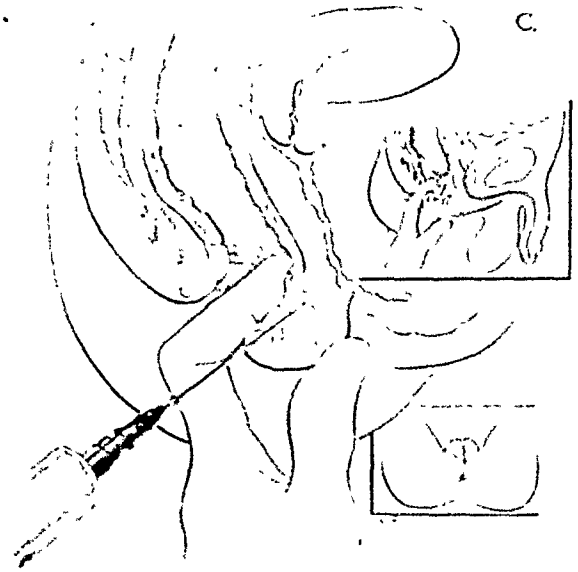


Fig. C. Technique of anterior anesthesia. The large figure shows induction technique in the female. The finger is only inserted for a short distance, up to approximately the first skin crease on its volar aspect. The pulp of the finger is hooked around (5) the anorectal ring. This can be seen lying in a much lower plane than this ring posteriorly. Posterior anaesthesia has already been induced, and the posterior musculature is shown relaxed with the anorectal ring flattened out. (1). The subcutaneous portion of the sphincter ani externus. (2). The superficial portion of the sphincter ani externus. (3). The deep portion of the sphincter ani externus. The sphincter ani internus can be seen lying under the pulp of the finger as a flat muscle.

Fig. C1. Inset—Shows the relation of the anal and anorectal musculature to the bulb of the urethra and other genital organs in the male. Note the distance from the bulb of the urethra, prostate and seminal vesicles. The needle is guided with the finger in the anal canal. In the female the needle is far removed from important structures. In the male the bulb of the urethra is at a safe distance from the area of anaesthesia. The section does not show the pubo-rectalis. Anteriorly this muscle has left the anal musculature and cannot be shown in this plane.

Fig. C2. Dotted area shows the field of anaesthesia induced by the anterior technique.

established the passage of a large bulky stool, (or digital examination roughly or hastily performed), may result in a tear in the lower end of the anal canal, usually in its posterior vulnerable area; then the lesion known as fissure is initiated. The patient who has become aware that liquifaction or softening of the stool is necessary in order to effect its easy passage, usually is fairly comfortable, but even now, for the first time, develops pain and will come seeking urgent relief. The careful, prudent patient may defer the formation of this fissure for months or years by the habitual use of salines or liquid paraffin; thus he may avoid trauma to the narrowed anal canal. In the end, however, the patient is no better off, because, ultimately, stenosis of varying degree will occur. Only too often will one encounter patients who present themselves with an oily-fecal leakage (usually observed when liquid paraffin habitually is taken) and in whom digital examination is not tolerated.

The crypts or pockets of Morgagni which lie just above the pectinate line are of little consequence in the normal subject, in fact are hardly visible during examination of the lower rectum. The passage of liquid or mushy stools is very irritating to the anal canal and one invariably finds reddening and congestion of the anal papillae, (which guard and crown the anal crypts) due to edema, and then easily can visualize the crypts. Retrograde pressure will elicit a mucoid discharge from the pockets and, in some patients, a frank muco-purulent or purulent exudate.

It must be remembered that the crypts of Morgagni mark the junction of the *proctodeum* with the hind gut, and the point of breaking down of the proctodeal membrane. In other words, nature has presented man with another one of its subtle pitfalls at the end of his embryological evolution. In some people, the crypts of Morgagni are very shallow and made out with great difficulty, in fact they may be regarded as almost absent. In such circumstances, one finds only a clean transition from squamous epithelium to columnar epithelium marking the area of anal crypts. In other patients, one finds well developed and deep anal crypts, and these are the cases that develop cryptitis when and if conditions become favorable. In certain instances, Hermann and Desfosses (6), Harris (7), and Lockhart-Mummery (8), have observed racemose, multiglandular structures running out from the bottom of the crypts of Morgagni into the peri-anal tissues. Infection of the crypts of Morgagni (7 and 8) with secondary infection of these glandular structures, these observers regard as the process in peri-anal suppurative lesions. These large multiglandular structures lined with secreting epithelium very frequently have been found in cases of peri-anal suppuration and fistula in ano. Like the crypts of Morgagni, these glandular structures are absent or very rudimentary in many people. In other words, embryologically certain people are by nature made susceptible and vulnerable to the establishment of a cryptitis and to perianal suppuration.

This description of the crypts of Morgagni becomes necessary, because where liquifaction of the stool is habitually indulged in, lodgement of bacterial laden residue in the anal pockets occurs soon or late. The patient now experiences spasm with or without fissure, accompanied by an active cryptitis. The whole picture becomes a vicious circle because the patient must continue the use of liquifying purgatives. Fortunately the infection does not too frequently travel beyond the stage of cryptitis; it is surprising that one does not oftener find peri-anal suppuration. The embryological observations of the authors mentioned above (6, 7 and 8), probably provide the answer to this. The necessity for the use of liquifying purgatives, where spasm has become established, immediately suggests itself to the average patient. This, at least temporarily, provides comfort and keeps the bowels open. There is another group of patients, who, for general health reasons, will begin to indulge in a morning dose of salts, or perhaps take salines at more frequent intervals. Then food residues are hurried through the intestinal tract and the patient begins to have one or more liquid, precipitous stools daily. Passive congestion then is produced in the superior haemorrhoidal veins, spasm follows, (the bulky stretching effect of the motion is lost), and a cryptitis, when the crypts are well developed, becomes established. Liquid paraffin in large doses habitually taken will accomplish a similar result. Thus, one cannot help but regard the ingestion of harsh purgatives, salines or large doses of liquid paraffin as having a deleterious effect upon the ano-rectum (3). The combination of ingestion of alcohol, with a harsh morning saline, habitually taken, has been observed to be a frequent precursor of the clinical picture above described.

Clinical Examination: Patients of this character easily are recognized upon examination. Spasm or

fibrosis of the anal canal is easily determined by digital examination. Where spasm or fibrosis is well established, the patient will not tolerate passage of the index finger. In such instances, passage of the small finger well lubricated and gently passed usually is successful. The presence or absence of fissure should be determined. Marked hypertrophy of the anal papillae often may be discovered. In some patients these are sufficiently prominent as to form actual polypi. One or more may be present. They must be regarded as the result of long standing irritation. The anal canal has a congested unhealthy appearance. Perianal pruritis often is present, particularly when frequent liquid stools have been experienced. In the average patient, it is impossible to pass a rectoscope or to perform sigmoidoscopy. Probably such examination will have to be deferred until anal spasm or stenosis have been overcome. However, in many patients, a rectoscope of small calibre (as that of Kelly) may be introduced. Bensaude's proctoscope is suitable for such cases. The Author has constructed a small tubular proctoscope, which is approximately slightly more than half of the diameter of the Gabriel proctoscope across its lumen. Through it one may see the lower rectum. Often, one will be surprised in such instances to find the ampulla filled with redundant mucous membrane and large varices covered by an unhealthy granular mucosa. These have not been extruded because of the sphincter spasm. They are evidences of passive congestion, straining and long continued purgation. When the spasm has been relieved and the patient's normal bowel habit has become established after a short time one may notice improvement in this mucous membrane redundancy and the varices will appreciably diminish. In many patients it becomes necessary to defer treatment of the mucous membrane redundancy and hemorrhoids.

TREATMENT BY CONSERVATIVE MEASURES BASED UPON THE PRINCIPLE OF REST

The treatment to be outlined essentially is ambulant and non-operative. It is based upon the surgical axioms of Hilton in his Lectures on "Rest and Pain" delivered to the Royal College of Surgeons in London, 1860, 1861 and 1862, and upon his teachings in Guy's Hospital, London, where he emphatically taught by lectures, and demonstrated clinically in the wards, the therapeutic value of mechanical and physiological rest in surgery (1).

Hilton based his reasoning upon anatomical facts and applied these facts to the needs of daily surgical practice. It is upon a thorough and scientific of the anatomy of the anal canal and ano-rectum, with the application of this knowledge, which forms the main premise upon which treatment of anal fissure, anal spasm and anal stenosis is carried out in this communication. Hilton emphasized the need for rest in lesions of the rectum. He states in his lectures that "rest is a most important therapeutic agent in the cure of accidents and surgical diseases". He states again "I depicted the instinctive promptings of nature to secure rest on the occurrence of accident or disease. Lastly, I attempted to shadow forth the different appliances for the attainment of rest with which that surgeon only will become familiar who has an accurate knowledge of the anatomy and physiology of the different parts which he may be called upon to treat." Hilton described dorsal ulcer of the anus. He described referred symptoms to the bladder, to the knee and thigh reflexes and to the genital organs, resulting from fissure. He emphasizes the need for physiological and mechanical rest to the sphincter. He recommends the recumbent position, soft diet and discussed the value of silver nitrate or bichloride of mercury to the fissure which forms an adherent albuminous defence to the raw surface and thus provides rest by covering the denuded surface and [illegible]. He regards albumen-coagulating agents for this reason as quite valuable. Where the ulcer had become chronic Hilton divided the sphincter fibres with the bistoury knife in order to secure mechanical and physiological rest.

The substance of this thesis is the presentation of a method of securing mechanical and physiological rest by the employment of oil-soluble anaesthetics in these lesions based upon a knowledge of the anatomy of the parts.

Oil-Soluble Anaesthetics. The use of oil anaesthetics in rectal surgery was first introduced by Yeomans, Gorsch and Mathesheimer in 1927 (9). These workers used a solution consisting of equal parts of para-amino-benzoyl-benzoate and phenomethylol in ninety parts of rectified sweet almond oil. They found this injection far superior to that of alcohol in producing anaesthesia for the relief of pruritis ani. Anaesthesia producing agents when dissolved in an oily base and injected into the tissues, produce a prolonged period of anaesthesia affecting the parts immediately injected and the nerves coursing through these parts with the areas supplied by them. The injection of anaesthetic substances dissolved in water will produce anaesthesia of only short duration; on the other hand the injection of oil-soluble anaesthetics (sweet almond or olive oil as the base) will because of the very slow liberation of the anaesthetic agent from its oily base and its slow rate of absorption, produce local anaesthesia and relaxation, *i.e.*, sensory and motor anaesthesia for varying periods. Such period may range from days to several weeks. If the induction is properly carried out, a profound local anaesthesia both sensory and motor may be obtained. During this time there is a complete interception of painful or uncomfortable stimuli and relaxation of the musculature, providing actual stenosis or fibrosis has not already become established.

In 1929, in London at St. Mark's Hospital, Gabriel (10) introduced a preparation known as "ABA," a 3% solution of anaesthesin, benzyl alcohol, 5%, and ether 10% in almond oil. He also introduced an alternate solution of "percaine in oil"; this consists of percaine, ½ of 1%, benzyl alcohol, 10% and phenol 1%, in olive oil. Gabriel found that these solutions produced profound anaesthesia when injected and were of decided value in chronic pruritis ani and in acute fissures. In chronic fissures, he considers that operative interference is necessary. This he accomplishes by dissecting out the anal ulcer together with a large wedge-shaped area of skin dorsally between the anal canal and coccyx; such may measure approximately 2¼ inches in length. This radical operation Gabriel performs so as to secure adequate drainage and to insure healing within the anal canal before external healing takes place. The patient's stay in hospital is approximately three weeks.

Morgan (11), in a recent paper published in the British Medical Journal, introduces a new anaesthetic-oil which he calls "Proctocaine." It consists of procaine base, 1½%, butyl-para-amino-benzoate, 6%, benzyl alcohol, 5% in almond oil. He regards this preparation as comparatively non-toxic. He finds that it produces profound anaesthesia lasting from seven to twenty-eight days or longer; that there is no immediate after pain following injection, and that the preparation is very well tolerated by the tissues. Morgan finds that this preparation produces excellent anaesthesia, and that it is very valuable or curative in chronic pruritis ani and acute fissure.

In acute fissure, Gabriel injects his anaesthetic oil into the external sphincter and to each side of it, and uses from five to ten c.c. of "ABA." The whole injection is given dorsally, just behind the centre point of the anal circumference posteriorly, and to each side of this into the sphincter muscle. Morgan points out the need for an adequate induction in treating anal fissure and pruritis ani by the injection of anaesthetic-oils. He observes that since the inferior haemorrhoidal nerve and the perineal branch of the fourth sacral lie deep in the postero-lateral aspects of the ischio-rectal fossa that it is necessary to anaesthetize this area. He further emphasizes the need for introducing anaesthesia up to the anorectal ring; this procedure is based upon the recognition of this anatomical structure. In anal fissure, Morgan's whole injection is carried out dorsally and dorso-laterally. He injects the posterior anal region up to the anorectal ring and includes the dorso-lateral aspects of the ischio-rectal fossae in his induction technique. He records satisfactory results and cures in acute anal fissure, and anal spasm; he has been successful with his anaesthetic oil in carrying out surgical procedures in the anal canal and lower rectum. He has also found that a preoperative injection of proctocaine to be effective in lessening post-operative distress in rectal operations, with his induction technique. He employs proctocaine throughout.

The Author has been employing the principles laid down by Morgan, but has found it necessary to go several steps farther in effecting a radical cure of anal fissure, anal spasm and anal stenosis by the method of

injecting anaesthetic solutions in oil. By the technique described below, the chronic fissure is brought within the realm of ambulant, conservative treatment as is also anal stenosis; in the past such lesions have been amenable only to radical, surgical measures.

AUTHOR'S TECHNIQUE OF TREATMENT, OF ANAL FISSURE, ANAL SPASM AND ANAL STENOSIS

Our observations are based upon an unselected series of approximately fifty patients, who, during a period of two years, presented themselves with the lesions of acute or chronic fissure, anal spasm or anal stenosis. The duration of disability ranged from several weeks, to months and years. Several of the patients had symptoms of many years' duration: it was not uncommon to obtain a history in which a middle-aged-patient would date discomfort back to adolescence.

The results secured by the technique to be mentioned uniformly have been good in all three lesions, regardless of the time duration of the affection. The cases of long standing who had chronic, well established changes, required more thorough and adequate treatment and after care, but in the end exhibited satisfactory and happy results. For this reason the Author believes it unnecessary to tabulate the various cases who presented the lesions in various stages of their evolution, and who were all treated by the same technique. The cases reviewed and treated are divisible into the following groups:

(a) *Acute anal fissure*, usually dorsal: simple muscle spasm is always present; (b) *Chronic anal fissure, usually dorsal:* the whole anal canal is fixed and there is an actual stenosis of the lumen. (Spasm replaced by fibrous changes of the anal and anorectal musculature, not relaxed under spinal anaesthesia); (c) *Anal spasm, without fissure:* these cases all show varying degrees of inflammation of the anal crypts of Morgagni and accompanying the cryptitis, the papillae crowning the crypts are edematous, inflamed and often hypertrophied, and (d) *Anal stenosis, without fissure:* these cases show a marked cryptitis and papillitis; the papillae may be polypoid; large redundant mucosae and varices (internal haemorrhoids) are sometimes present above the stenosed anal canal and not extruded because of the very narrow and fixed anus; pathology as shown (c) and (d) may at any time develop fissure in ano.

After the anal diameter has been returned to normal or near normal, the patient may for the first time extrude the mucosal redundancy or the haemorrhoidal tissue. *The hemorrhoids may subside after a time* or may need to be dealt with by submucous injections or operation (12). The etiology and evolution of these lesions already has been discussed.

The anaesthetic oil employed in the majority of the patients has been the English "ABA." About a year ago the anaesthetic components of the original preparation were somewhat modified and the preparation became known as "ABA No. 2." This was supplied by Allen and Hanburys, London, when ordinary ABA was asked for and replaced the original ABA. This newer preparation appeared to have a more positive action and to give a somewhat longer period of anaesthesia. Gabriel's percaine in oil was early discontinued. Several sloughs were encountered unless the solution was placed deeply; this is not always possible. Such reaction was regarded as due to its 1% phenol content, and never once was a slough encountered with the old or newer ABA. For the past few months, Morgan's "Proctocaine" has been given a trial to the complete exclusion of ABA. This also is supplied by Allen and Hanburys-London, and appears to compare very favorable with ABA No. 2. It has at least two advantages over ABA No. 2 as evident to the writer in the short time that it has been employed. It produces a more immediate anaesthetic effect (ABA *may* take several minutes longer before anaesthesia becomes established) which appears to be more thorough and marked than even the newer ABA. Minor surgical operations may be carried out in the anal canal under this anaesthetic oil. This is a great advantage. The anaesthesia is more prolonged than either the old or new ABA. It is not unusual to find that the anaesthetic effect persists after two, three and four weeks. The preparation appears to have a very low degree of toxicity. Doses of five to fifteen CCs are well tolerated and no untoward effects have thus far been observed. The writer feels from his short experience with this preparation that "Proctocaine" as an anaesthetic oil is superior to ABA and has distinct advantages over these older preparations known as ABA, and ABA No. 2.

(a) Acute anal fissure (dorsal). In this lesion, posterior and postero-lateral anaesthesia is induced embracing the whole of the anal and anorectal musculature posteriorly, together with the posterior half of the ischio-rectal fossa bordering upon the anal canal laterally. This will include the postero-lateral aspect of the ischio-rectal fossa across which run the inferior haemorrhoidal and perineal nerves.

Technique. The patient lies on the right side in the right Sims' position with the knees drawn up at the edge of a firm table. The operator sits on a low stool opposite the flexure of the patient's knees at the lower end of the table. The area is shaved and cleansed and prepared with spirit and tincture of "metaphen." A skin wheal is raised with 2% novocaine at a centre point of the posterior peri-anal area just at the outer border of the subcutaneous portion of the external sphincter. A one or one and a half inch hypodermic needle of the smallest available bore is employed in raising this wheal. A few minims of the novocaine are now injected into the deeper skin layers dorsally, into the deeper subcutaneous tissues and into the outer subcutaneous sphincter fibres. In all about one to one and one-half cubic centimeters of 2% novocaine may be employed. This preliminary detail makes the subsequent puncture and penetration by the larger needle quite painless. Quite often the patient will feel nothing further after this. A two and one-half or three inch length, size 20-21 gauge needle with a 10 c.c. Luer, lock syringe is ready. A short size, 18 gauge needle is available for sucking up the oily "proctocaine" into the syringe. The proctocaine is placed in the hot steriliser and warmed for several minutes or it may be placed in hot water for a few minutes. The syringe is now loaded and the long two and one-half to three inch needle locked into the syringe. As shown in Fig. 1 the lubricated left index finger is placed in the anal canal with the volar aspect (pulp) of the finger pointing dorsally. The end of the finger is hooked around the ridge of the anorectal ring which lies approximately two inches from the anal opening. The finger is inserted to the second skin crease. The needle must be at least two and one-half to three inches in length because one must inject up to and including the anorectal ring, and at least half to one inch of working needle must be available. It is unwise to plunge the needle up to its hilt, unless an extra guard is present as in intra-spinal needles. For this reason a longer needle provides safety. The needle is advanced through the skin wheal and the oily solution is slowly injected. It is kept about a quarter to half an inch away from the anal canal and care must be taken that the needle does not perforate the anal canal or lower rectum. The fibres of the subcutaneous portion of the external sphincter are first injected. As the needle advances the operator perforates a fibrous resistant layer. This is the anal intermuscular septum, i.e., the lower fibrous portion of the longitudinal muscle of the bowel. The lower border of the internal sphincter is now injected. The needle advances further and enters the superficial portion of the external sphincter. The oily solution is injected right into these muscles. The needle again advances into the deep portion of the external sphincter. The injection is slowly and evenly continued. The puborectalis portion of the levator ani is now entered where it joins with the deep portion of the external sphincter and the longitudinal muscle fibres of the bowel to form the anorectal ring. The anorectal ring which up until this time has maintained its identity, in that the finger has remained hooked around its ridge in the anal canal as a definite entity, now dissolves so to speak away under one's finger and becomes flattened out. This is what determines whether one has reached and injected the anorectal ring with its levator fibres. Unless this succeeds adequate relaxation will not be obtained. This, doubtless, is a frequent cause for failure to cure an acute fissure by the injection of anaesthetic oils. One must inject deeply until one is certain that one has anaesthetized this anorectal

ring. The criterion of this consists of its disappearance and flattening out under the pulp of the left index finger in the anal canal. The needle is now not completely withdrawn but only up to the original skin puncture. Approximately five CCs of the oil anaesthetic have thus far been utilized. The finger is now turned laterally facing the left ischio-rectal fossa. The subcutaneous portion of the whole posterior and postero-lateral half of the ischio-rectal fossa is injected with the anaesthetic oil. As one approaches the anal canal in its lateral aspect some of the musculature which is not yet relaxed will be included in the injection. The right ischio-rectal area, *i.e.*, the right lateral portion of the anal canal and its bordering fossa are likewise injected in turn, by turning the pulp of the index finger to the right and guiding the needle to the right ischio-rectal region. After the ischio-rectal fossae (and their coursing inferior haemorrhoidal and perineal nerves) have been anaesthetized the needle is pointed in the same plane as the anal canal and a few CCs of the solution injected into the lateral peri-anal masculature as deep as the anorectal ring. (Approximately a depth of two inches) 2.5 to 5 c.c. are employed in each lateral injection, the total injection totalling 10-15 c.c. Following a satisfactory induction, the spastic anal canal has become relaxed and digital examination can be painlessly and deliberately performed. The tissues surrounding the anal canal in its posterior and both lateral boundaries now is massaged for several moments by gentle external pressure. At no time must a subcutaneous bulge be visible during the injection, in other words one must avoid pooling in the subcutaneous tissues.

The next step is very important. One waits about five minutes keeping up firm massage in the *interum*. Both index fingers are now well lubricated and inserted through the anal canal to the height of the anorectal ring, the backs in apposition and the pulp of both fingers facing laterally. The whole of the anal canal, including the anorectal area, with its surrounding musculature, is now gently dilated until one can easily insert a large proctoscope or three fingers. This stretching is at first resisted by the patient, who perceives no pain, but is conscious of the stretching force. If this is previously explained the patient will not attempt to resist this gentle dilatation which although uncomfortable is not painful. Under combined anterior anaesthesia to be dealt with, this dilatation is much facilitated and more easily carried out.

The fissure is painted with 5% mercurochrome and the patient seen every day. A small pledget of absorbent cotton is placed over the anal orifice and if gently teased out will stay in position. A drop of ichthyol or balsam of Peru is placed on the fissure every day with a wooden applicator and the well lubricated index, middle finger and thumb or graduated bougies (St. Mark's) are daily passed to maintain the dilatation and to encourage healing.

After-care A hot hip bath the night of the same day as the injection and a hot tub every second day is recommended and helps in the healing of the ulcer. The hot hip bath following the injection prevents pooling of the injected oil anaesthetic and gives the patient much comfort. There is usually no pain following the induction, especially since the advent of proctocaine. All purgatives are discontinued. The patient is placed upon a normal diet and encouraged to have natural bowel movements without assistance. The passage of a bulky, formed stool is desirable and the habit of passing liquid or mushy stools under the stimulus of purgation, must be early broken. It may take some time before the patient's stools again become formed, because, preoperatively, the bowel may have been much irritated. "Normacol" crystals or "Metamucil" (Searle) are very helpful in those cases whose stools continue loose or mushy. A dessert-spoonful at bedtime in water is a satisfactory dose. The patient is watched until the fissure has completely healed and no further spasm is present. This may take several weeks or a month, during which time the anaesthesia usually persists.

(b) Chronic anal fissure. Posterior and postero-lateral anaesthesia is induced as described under acute fissure. After induction, digital examination is quite painless and there is some discernible relaxation of the anal and anorectal musculature. The anal stenosis may be the result of spasm as well as fibrosis, and therefore where the chronicity is not too well established, a degree of relaxation will be elicited by the dorsal anaesthesia. The next step consists of a careful examination of the fissure. If possible this should not be disturbed. The anterior anaesthesia *(vide infra)* with its resultant relaxation, together with the daily after-care will more often than not result in healing of the lesion. The posterior anaesthesia induced by the "proctocaine," is usually ample for any intra-anal minor surgical procedures. Any dissection of perianal skin, outside the anal canal, may require a few drops of 2% novocaine. Obvious interference with dorsal drainage at the base of the fissure, such as by a sentinel skin tag (sometimes present in very chronic fissures, the result of anal contraction) should be attended to by simple ablation of the tag. In certain cases the lesion has become cartilaginous. Simple trimming of the edges of the fissure with eye scissors should be carried out. If the base of the ulcer has become undermined to form a superficial subcutaneous tract, this will require to be laid open. Any large hypertrophied papilla which prolapses or which forms the apex of the fissure should be crushed and snipped away. Seldom should it be necessary to dissect away the lesion. No perianal skin is cut away, with the exception of a "sentinel," dorsal tag, if one be present. Whenever possible it is advisable to carry out posterior and anterior anaesthesia, without practising any surgical procedure. Should healing of the anal lesion fail to occur after a month and symptoms recur, then one may lesion fail ot occur after a month and symptoms recur, then one may dissect out the fissure under posterior anaesthesia, followed by the anterior block at once or within forty-eight hours. Patients will be seen whose anal circumferences have been restored to normal but in whom the dorsal ulcer has been replaced by a firm, painless cicatrix. This is the result of the chronicity of the lesion and nothing further need be attempted. Bowel movements are comfortable and the motions are formed and bulky. Following the induction of anaesthesia, careful after care to the fissure, such as daily applications and the passage of bougies, is essential.

The next important step consists in the induction of anterior anaesthesia. This may be done immediately following the posterior induction or deferred for two or three days. Where any intra-anal surgical procedure has been carried out, it is better to defer the anterior induction for several days. Although some measure of relaxation may have been elicited by the posterior induction, this is immediately lost should any intra-anal surgical procedure be performed. The remaining portion of the anal and anorectal musculature anteriorly which is still unanaesthetized, has responded by spasm, consequent upon the operative procedure. This is taken care of by the anterior induction, when relaxation results at once, or is easily established by gentle dilatation, which is well tolerated.

After-care: The patient whose duties are not too onerous may continue at work after anaesthesia has been induced. When minor surgery has been practiced, or when the injections tire the patient, a day or two of rest at home is advisable. Long motor journeys or vigorous exercise should be forbidden for some weeks. Robust patients do not mind the induction of the anaesthesia in the least. Nervous, frail people may be somewhat upset, and should rest around the house for a day or two taking a daily hot hip bath in the *interim*.

Anterior anaesthesia is carried out as follows: The patient lies on the left side at the edge of the table in the left Sims' position with the knees drawn up. The operator sits at the end of the table opposite the flexure of the patient's knees. The skin is prepared as for posterior anaesthesia. A novocaine wheal is raised at the centre point anteriorly just in front of the skin overlying the subcutaneous portion of the external sphincter. The subcutaneous tissues deep to this are infiltrated with about half to 1 c.c. of the 2% novocaine solution. This skin wheal in the male corresponds to the area between the outer border of the subcutaneous portion of the external sphincter and the central point of the perineum, and in the female to the area between the outer border of the subcutaneous sphincter muscle and the beginning of the perineal body. The lubricated left index finger is gently inserted into the anal canal with the pulp of the finger facing the prostate in the male and the vagina in the female. It must be remembered that the anorectal ring anteriorly lies at a distance of approximately one inch from the anal orifice, corresponding roughly to the height of the first skin crease on the volar aspect of the index finger. This represents the height of the area of anesthesia. A one and a half to two inch 21 gauge needle is employed for this anterior injection, in contrast to the two and one-half to three inch length for the posterior injection. In the male the base of the prostate is felt just above the anorectal ring, and in the female the back of the cervix can usually be palpated. The bulb of the urethra in the male is a fair distance anteriorly and superior to the anorectal ring, and there is very little danger of reaching this structure if one recognizes the height of the anorectal ring and has an approximate idea of the relation of the bulb of the urethra to the central point of the perineum. To each side of the anorectal ring the puborectalis portion of the levatores ani muscles can be felt leaving the anal canal, running forward. It will be remembered that anteriorly the anorectal ring is formed by the fusing of the deep portion of the external sphincter and the longitudinal muscle of the bowel, reinforced medially by the inner circular muscle fibres of the bowel (upper border of the internal sphincter, which is really a flat and not an annular muscle band). The ring anteriorly, because of the absence of the puborectalis in its formation, is not so prominent as posteriorly.

A 10 c.c. Luer lock syringe is loaded with the Proctocaine solution. The needle passes through the skin wheal and enters first the fibres of the subcutaneous portion of the external sphincter. It passes quite superficially through the fascia of the longtitudinal muscle which is inserted beneath the skin of the anal canal to form the anal inter-

muscular septum. Next the lower border of the sphincter ani internus is entered. All this time the injection is being continued with a slow even pressure. The lower border of the superficial portion of the external sphincter lies only a millimetre or two above this and is soon entered. This is next injected. Next one enters the deep portion of the external sphincter muscle as it enters into the formation of the ano-rectal ring. One has now only traversed a distance of approximately one inch. In the male the anorectal ring is just below the base of the prostate and in the female this lies below the level of the cervix uteri. The needle is now slightly withdrawn and pointed in an anterolateral direction to each side of the middle line and one now injects the fibres of the puborectalis portion of the levatores ani muscles as they leave the ano-rectum. In all one injects only about 5 c.c. of the anaesthetic all arterially, because one has less area to traverse and therefore less to anaesthetize. In pregnant women who suffer from rectocele one will not attempt to inject the puborectalis muscles, which are in such cases retracted or absent. In such cases one stays within the thinned rectovaginal septum while injecting into the anal and anorectal musculature.

After anterior anaesthesia has been induced one may recognize a measure of real relaxation even in those cases that have a well developed fibre of the anal and anorectal musculature. The anaesthetized levatores ani muscles (puborectalis) permit the anal canal to fall away as it opens, and the anaesthetized short anal canal arteri shows at once a full measure of relaxation. Full dilatation as described under posterior anaesthesia is now completed and where too little relaxation has been experienced, a slightly firmer stretching force is exerted for several minutes. Anaesthetization by this technique of the short anal canal arteriole with relaxation of the levator group affords a full measure of relaxation, particularly so if dilatation has been exercised. When anterior anaesthesia has been induced a moderate degree of dilatation should be practiced. This is very beneficial. Relaxation may be so complete that one may have misgivings about the patient's continence during the duration of the anaesthesia (2 to 4 weeks). Even after full dilatation, one has very little difficulty on this score. Attention is directed to the formation of bulky faecal stools as already described and all laxatives are forbidden.

Section of the external sphincter (really only its subcutaneous part) has been described by some authors as adequate in dealing with spasm and chronic fissure. Its application has been criticized. One is dealing with a lesion of the whole anal and anorectal musculature (or an anal fissure which may be part of the levatores sphincter complex) to be truly relieved. By the Author's technique one gently stretches (quite different from forcible dilatation) under adequate anaesthesia a completely anaesthetized and resting anal and anorectal musculature. One very rarely encounters bleeding and in the Author's cases it has never been necessary to catheterize any of the cases. There is a very different between faecal distension of the anal canal as it sometimes part vomit under general anaesthesia or even spinal anaesthesia and the gentle stretching of a completely relaxed and anaesthetized musculature. During this gentle dilatation one can actually feel the tissues give way. Slight tears of the anal skin which have become adherent and contracted are of no consequence and heal within a few days. If the rectal infection follows the posterior anaesthesia by several days dilatation can still be comfortably carried out at the end of this time.

Although it is wise to carry out a preliminary posterior block before attempting the anterior anaesthesia, this is rarely impossible. There may be an infected dermal area in very chronic fissure or submucous pyogenic external. In such cases anterior anaesthesia without posterior injection directed at the short submucosal canal anteriorly has been found to give splendid relaxation and permit complete visualization and local treatment to the fissure. In anterior fissure although the nerve supply to the anal canal is not intercepted by anaesthetizing the *ischio-rectal fossae*, and although it will not control the pain of a dorsal ulcer, nevertheless one can produce anal relaxation and thus permit treatment and topical application to the lesion which hitherto has been out of sight because of spasm or fibrosis. In anterior fissure in ano simple anterior anaesthesia is adequate, with the usual after care of the lesion.

(c) Anal spasm. In cases of simple spasm, posterior anaesthesia alone or supplemented by anterior anaesthesia is sufficient to secure relaxation. Gentle dilatation is practiced. Any large hypertrophied papilla which prolapses down is crushed at its base and nipped off. The finger or bougies are passed daily. It may be wise to interdict alcohol and condiments for a time. No attempt is made to cut down or lay open any of the infected crypts (cryptotomy). This is a procedure of very questionable benefit *especially in the light of the work* already quoted (6, 7, and 8). With the relief of the spasm followed by sufficient after care, there is eventually a marked improvement of the cryptitis. Edema of the papillae subsides, the crypts and anal canal lose their contested appearance and discharge from the pockets if present ceases or is lessened. The case is followed for six to eight weeks and seen at least two or three times a week and if possible daily for at least the first fortnight. The openings of the crypts are touched up with 5% aqueous mercurochrome at every visit. Simple massage of the finger or bougie empties the pockets of any discharge by retrograde pressure.

Aftercare. Any soothing ointment is ordered for the anal canal. The passage of bulky formed stools is very beneficial. Nothing further is done. This plan has been quite adequate and infrequently after several months may need to be repeated once. Once the lumen of the anal canal has been returned to normal there appears to be very little tendency to a return of the spasm.

(d) Anal stenosis. This lesion is dealt with by combined posterior and anterior anaesthesia together with adequate dilatation. The cryptitis is dealt with as under (c). A reasonable period of after care is insisted upon together with the regular passage of bougies. It is frequently necessary after a few months to repeat the anaesthesia. Once the lumen has been returned to normal there is little tendency for recurrence.

SUMMARY AND CONCLUSIONS

A study of anal fissure, anal spasm and anal stenosis is presented. The evolution of these lesions is described.

The anatomy of the anal canal and ano-rectum is presented because of its important bearing upon treatment.

Treatment is based upon the principle of Hilton, namely, the securing of adequate mechanical and physiological rest to the affected parts. Based upon the principle of rest, the Author has presented his plan of treatment.

The carrying out of the described technique necessitates careful attention to anatomical structures and landmarks.

The treatment is essentially conservative and ambulant, and in the Author's experience has greatly reduced the number of cases which need to be treated by radical surgical measures.

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SECTION VIII—*Editorial*

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastro-enterological Association is in no way responsible for editorial expressions.

ENDEMIC DYSENTERY: SIGNIFICANCE AND DIAGNOSIS

ENDEMIC dysentery is a common occurrence in this and probably other countries. In the past summer alone, there were six outbreaks of endemic diarrhea in summer camps of New York State which were traced to dysentery or dysentery-like organisms. Attempts have frequently been made to link up this constantly recurring bacillary dysentery with the increasing incidence of ulcerative colitis. Certainly if there is such a disease as chronic bacillary dysentery it is pathologically and probably clinically indistinguishable from what we now recognize an "non-specific" ulcerative colitis.

But what constitutes a diagnosis of dysentery, particularly in the chronic form? Rarely are we sufficiently fortunate to find a positive stool culture. Phage is unreliable as a diagnostic phenomena; serum agglutination is open to wide variations of interpretation.

In this issue of the *Journal* an article in the nature of a critique has been offered by Dr. A. Penner in which he surveys, in a dispossionate and scientific manner, the natural limitations of the diagnosis of dysentery, thus defining one of the premises to a possible relationship between the two diseases, *e.g.* nonspecific ulcerative colitis and endemic dysentery.

Dr. Penner particularly calls attention to the interpretation of the specific agglutinins in the serum of the patient. Carelessly, many physicians place a diagnosis of dysentery upon agglutinations of 1:40 to 1:80. The unreliability of such a diagnosis is well known to all professional pathologists, but not usually understood by practitioners.

The caution and warning contained in Dr. Penner's article regarding such an interpretation are emphasized and deserve most careful reading.

Burrill B. Crohn, New York City.

A BOLD SUGGESTION

ELMER H. BOBST, President of Hoffman-La-Roche, Inc., writing in "Roche Review," offers a tentative solution for a number of medical economic problems, by making the suggestion that all the recognized and ethical pharmaceutical houses band together and subscribe a very large sum of money each year which would be placed at the disposal of the A.M.A. for the sole purpose of ethically advertising the medical profession via broad radio hook-ups at the most preferred hours, once weekly, using types of programs second to none now in use. Such a program, Mr. Bobst believes, would do a great deal to divert money now spent on patent medicines into regular ethical channels and thus frankly into the coffers of the ethical pharmaceutical firms too. The source of the funds would not, under Mr. Bobst's plan, be revealed to the public. Furthermore he makes the point that such a program might have a deterring effect upon the possible establishment of controlled medicine. He gives evidence of sincerity in promising from Hoffmann-LaRoche $20,000 annually for the next five years, provided other firms of repute contribute equally. Surely this suggestion of Mr. Bobst's is something at least to provoke thought among physicians. It seems unlikely however that our present code of ethics could sanction such a proposal. Nevertheless circumstances alter cases and we are living in an age when new fashions in many of our sociological garments are more than noticeable.

Beaumont S. Cornell, Fort Wayne.

GASTRIC ACIDITY AND ERYTHROCYTE COUNT

To the Editor:

IN an article under the title "The Relation of Gastric Acidity to the Erythrocyte Content of the Blood" in your issue of September, 1936, Apperly and Cary state that it was Apperly and Crabtree who showed in 1931 that the concentration of HCl in the human stomach after a test meal was regulated by the CO_2 content of the plasma of the fasting subject, and furthermore that this was found to be true also when different normal individuals were compared.

I wish to call your attention to the fact that this observation was made and described first by me (*Klin. Woch.*, 3:1951, 1924), and that I subsequently enlarged upon this subject in several publications (A New Approach to Dietetic Therapy; Metabolism of Water and Minerals and Its Disturbances, Boston, 1933; *The Lancet*, 1:1035, 1936, etc.). I showed in addition that in reality it is the concentration of all the acid substances in the blood, rather than that of CO_2 alone, that in accordance with the rules of physicochemistry, influenced the concentration of HCl in the gastric cavity. The acid substance of the blood which is quantitatively most important is CO_2 and since the variations in the concentration of this acid are the most common occurrences, in most (but not all) cases a parallel behavior might be found between its concentration in the blood and the gastric acidity.

Other statements made by Apperly and Cary are that there is a relationship between the gastric acidity and the red cell content of the blood and that anemia can bring about achlorhydria so that in certain conditions where anemia is associated with achlorhydria, the entity which they call "anemic achlorhydria" must be considered in addition to "achlorhydric anemia." These observations also were first published by me in the year 1924. In one publication (*Zeitschr. f. d. ges. exp. Med.*, 41:342, 1924) I described my findings in a statement, according to which the higher the percentual volume of the red blood cells in the whole blood ("hematocrit value") the higher the gastric acidity. The existence of this relationship was explained by the observation that both the hematocrit figure and

the gastric acidity are governed by the concentration of the acid substances in the blood.

Mention should be made, however, of the fact that the red blood cells behave in the blood as acid substances so that not only are these former influenced by the concentration of the latter, but that the red blood cells in their turn influence the concentration of the acid substances in the blood, hence influence the gastric acidity as well. Consequently a hypochlorhydria or achlorhydria may follow if there is a decrease in the red blood cell content of the blood, an occurrence which I described in 1924 as "hematogenous hypochlorhydria or achlorhydria" *(Zeitschr. f. d. ges. exp. Med.,* 43:247, 1924), and to which Apperly's "anemic achlorhydria" corresponds.

Eugene Földes, New York City.

DR. APPERLY'S REPLY

DR. Foldes has raised the question of priority in two matters:

(1) The relationship of the CO_2 content of the plasma of the fasting subject to gastric acidity in a subsequent test-meal. In 1921, Bennett and Dodds (1) showed, as incidental to their main theme, a parallelism between the fasting alveolar CO_2 and a later gastric acidity. In 1922 Kauders and Porges (2) published similar experimental figures. In 1924, Foldes quoted these figures in a paper *(Klin. Woch.,* 1924, 3, 1951) and proceeded to build up a theory of secretion without however, up to that point, mentioning any experimental work of his own on either alveolar or plasma CO_2, or even quoting the source of the above figures in his book ("A New Approach to Dietetic Therapy"). In 1927, Semmens and I (3), knowing that plasma CO_2 generally, but not always, parallels alveolar CO_2, and would be less liable to variation in short periods of time, decided to determine if a similar parallelism existed between plasma CO_2 and gastric acidity. Our results, elaborated by Crabtree and myself (4) in 1931, showed this relationship to be a very close one. *These facts do not bear out Foldes'* claim to priority.

(2) The relation of gastric acidity to red cell content of blood. In his paper *(Zeitschr. f. d. ges. exp. Med.,* 41:342, 1924) Foldes deals only with variations in acidity in people with a *normal* red cell count (this normal figure or its limits are not stated in the article referred to), regarding hematocrit variations as indication of swelling or shrinking of red cells, *i.e.* as due to variations in *"acid valencies"* ("saueren Valenzen") of the blood. This is a matter entirely different from our work. Cary and I (5) were concerned with the relation of gastric acidity to *red cell count* of blood, using our much larger hematocrit variations as indications of *anemia* or *polycythemia.* Nowhere in the paper referred to above does Foldes show any figures or refer to any such relationship as that shown by us. *Again, it seems to us, Foldes fails in his claim to* priority.

Frank L. Apperly, Richmond, Va.

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SECTION IX—*Book Reviews*

(This section is open to contributions from any medical reader, whether or not a member of the Editorial Council).

"Disturbios do transito duodenal," G. S. De Paula E. Silva, M.D. Published by Graphica Queiroz Bregner, Bello Horizonte, Brazil, 1936. Price, not stated.

DR. De Paula E. Silva has written a very creditable and easily readable monograph on disturbances in and, particularly, slowing of the transit of material through the duodenum. After reviewing the literature, he analyzes the findings in eighty-seven cases which were discovered during the examination of 800 patients with digestive disturbances. To many North American observers, this would seem too high an incidence, but doubtless the more carefully one looks for these things the more often they can be found. The big problem is how much significance to attach to them. Here in the United States, most men pay little attention to them unless they can be demonstrated on repeated examinations. *Certainly it rarely pays to* operate to correct them.

Dr. De Paula E. Silva believed that in a good many cases the changes observed were due to a certain amount of duodenitis and some of the stagnation may have been due to pressure by an abnormal mesenteric root. In general, the outlook is not serious and, as already stated, it is rarely necessary to operate. As the author wisely says, the treatment depends on the necessities of the individual case.

Most of the patients seen were young. There were frequent intervals of freedom from symptoms. Many of the patients had mild colicky pain, usually after meals. As one would expect, this pain was usually in the upper part of the abdomen. Unfortunately, the symptoms were commonly those of many types of organic and functional digestive diseases and there was nothing very characteristic about the syndrome observed.

Such a piece of work would be creditable if it were done by someone in a large center of learning so it is particularly creditable when done by a young man living in a small city far from the mental stimuli and the helps which come from association with able men in a large university.

Walter C. Alvarez, Rochester, Minn.

SECTION XII—"*The Clinic*"

Multiple Primary Melanomas of the Small Intestine

By

FRANK R. MENNE, M.D., F.A.C.P.*

and

J. A. P. BEEMAN, A.B.

PORTLAND, OREGON

MELANIN-producing tumors are confusing structures wherever they are found, but when present in the gastro-intestinal tract, they excite additional interest because of their extreme rarity here and the difficulties that arise in explaining the manner of their formation. Summarizing statements in the literature generally point out that melanotic tumors are most frequently found in the rectum, less often in the intestine, occasionally in the gall bladder, bile ducts, esophagus and mouth. In all of these, there arises the doubt as to whether they are primary or secondary manifestations.

Next to the rectum, the small intestine seems to be the most frequent site for melanomas. Thus far, there has been reported a small number of seemingly authentic instances of such primary tumors, namely by Trevis (1) quoted by Libman, Vander Veer (2), Kellert (3), Cox and Sloane (4), Peritz (5), and Lung (6). In view of their seeming rarity and because of the numbers present, it is deemed advisable to report the following case of multiple melanotic tumors of the small intestine.

CASE REPORT

H. V., an iron worker, aged 35, born in Oregon, of Dutch descent, was employed and in good health until March, 1935. At this time he began to feel fatigued and to lose weight (30 pounds in 4 months). This was followed by pains in the "pit of the stomach," associated with nausea and vomiting. His bowels moved regularly. At the time of the patient's admission to the Veterans' Administration Facility, Portland, Oregon, he weighed about 200 pounds, his pulse was 170, blood pressure S-110, D-70. There was tenderness over the epigastrium, a soft mass could be felt above the umbilicus. *The X-ray examination* disclosed an uneven defect at the base of the duodental cap with persistent raggedness of the pylorus suggesting an infiltrative pathological process. The patient began to have mental symptoms which led to the diagnosis of tumor of the abdomen, type undetermined, and *dementia precox, hebephrenic type.*

During his confinement in the hospital, his temperature varied between subnormal and 102° with synchronous variations in the pulse and respiration. The pulse rate was always above 90 and most of the time above 100.

Examination of the blood disclosed a progressive secondary anemia (RBC 2,760,000) and a relatively high white count (10 to 12,000). The feces contained occult blood. Gastric analysis revealed a combined HCL of 6, but no free hydrochloric acid, lactic acid being present. No noteworthy changes were present in the urine except for a trace of albumin and a relatively high specific gravity (1.025). On August 28 he was given 500 c.c. of blood. On September 4 an *exploratory laparotomy* was performed (Dr. George E. Pfeiffer), at which time multiple melanotic tumors were observed in the small intestine. This finding was confirmed by a biopsy of a mesenteric lymph node. Following the operation, the patient complained of gas pains, vomited bile, became distended, dyspneic, weak, and died on September 6, 1935, about 9 months after the onset of his symptoms.

The autopsy was performed by one of us (F.R.M.) and revealed the following pertinent pathological changes: multiple melanotic tumors of the small intestine; metastatis melanoma of the mesenteric and omental lymph nodes; metastatic melanoma in the spleen, heart and skin; hypostatic broncho-pneumonia, bilateral; fatty liver; acute emaciation. Further pertinent details were noted as follows: 'When the subcutaneous fat is exposed in the usual midline incision, firm, coarsely lobulated, moderately oily fat is seen, measuring about 2.0 cm. in thickness. When the peritoneum is opened, the intestine bulges upward as if under pressure. The great omentum is found adherent to the peritoneum opposite the surgical incision by fibrinous adhesions. The edges of the surgical wound are roughened, covered with some fibrin and small clots of blood, but healing has not yet fixed them together. The small bowel is of increased caliber; it is greater than that of the large bowel. There are also noted moderate constrictions with ballooning and blackish discoloration of the small bowel. There are a few scattered small, bluish-black, cyst-like bodies in the omentum. In the right upper quadrant, just below the gall bladder there is a large, firm, bluish-black mass. Similar masses are found in the second portion of the duodenum. There are no noteworthy changes in the pylorus. It has a circumference of 4.0 cm. The mucosa of the first 8.0 cm. is intact. The latter has a circumference here of 7.0 cm. Immediately below this there appears a circular, friable, black, fungoid mass that is 11.0 cm. in circumference, 6.5 cm. in width, and about 3.0 cm. in thickness. The mucosa over its surface has been denuded and ends sharply and bluntly at its elevated margin which is about 1.5 cm. above the level of the mucosal folds. The second and third portions of the duodenum are dilated, the circumference being 11.0 cm. There are seen here knob-like or shell-like, flat depositions of

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Submitted September 28, 1936.

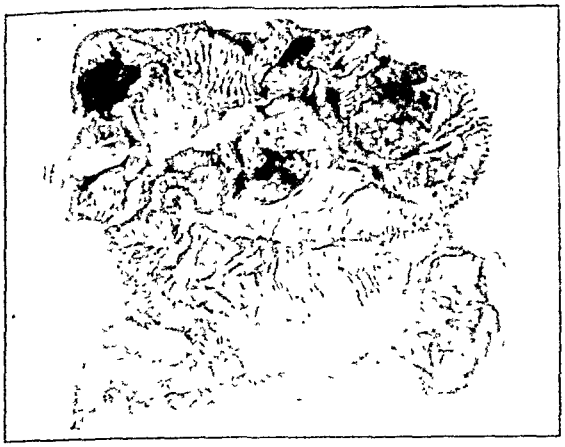


Fig. 1. Autopsy 37-9-35 (H. V.). Photograph of the small intestine showing the character, extent, size and effect of the melanotic tumors of the small intestine. A, upper end, B, lower end, T, larger tumors with superficial black craters.

pigment similar to the pigment seen in the large tumor mass just described. About 17 such small tumors are found in this area, lying between the first large tumor mass and the second which is in the jejunum 10.0 cm. from the ligament of Tritz. This second tumor mass is also circular, similar to the first, somewhat saddle-shaped and measures 7.0 by 7.5 by 4.0 cm. in size. The lumen of the bowel here is 13.5 cm. in circumference so that a small lumen remains in this tumor bed. Now below this second tumor mass there are found six small, knob-like, pigmented nodules that lie in the mucosa, most frequently projecting from the summit of a mucous fold, the mucosa terminating abruptly with serrated edges at the border of a crater that is black. A third large tumor mass is found to lie 14.0 cm. below the second one. This has its longitudinal axis and circling the lumen for a distance of 6.0 cm. It is somewhat boot-shaped and its widest portion is 3.5 cm. The mucosal border is slightly overhanging. There is seen projecting from the center of this defect a fungoid mound, with a broad, sessile base and a granular, slightly irregular surface. It extends upward for a distance of 2.0 cm. and is 2.5 cm. broad. The lumen of the bowel here has a circumference of 11.0 cm. There are three smaller, similarly distributed nodules, the largest 1.5 cm. in diameter immediately below this. Between this third tumor and a fourth large mass, which is 20.0 cm. farther down, there are 9 similar, smaller, black, fungoid masses on the summits of mucous folds and for the most part in line with each other. None of them is over 1.5 cm. in diameter. Now the fourth and largest of the fungoid masses is that which was found lying in the right upper quadrant, apposed to the gall bladder and extending into the transverse mesocolon and is fused rather tightly to the transverse colon near the hepatic flexure with fibrous connective tissue bands that are so dense as to make separation of small portion of bowel, and yet there is no evidence of invasion into mucosa of the colon. This large fungoid mass is covered with serosa and the fused leaves of transverse colon. It projects out pouch-like from the upper surface of the jejunum. The extra intestinal mass measures 12.0 by 6.0 by 12.0 cm. in various dimensions. It communicates with the lumen of the bowel by an irregular, circular, ulcerating opening from which dirty, greenish-gray to yellowish-brown, friable, fungoid masses project. The opening has a maximum diameter of 8.0 cm. (See photograph T4). The circumference of bowel here is about 14.0 cm., while immediately above it is about 15.0 cm. and immediately below it is 8.0 cm. Just below this fourth tumor mass there is seen a rather large, mushroom type of growth that is 5.0 cm. in diameter and is attached to the mucosa of the bowel by a sessile type of pedicle that is only 2.5 cm. in diameter. The overhanging bulk of this tumor mass rests upon normal surrounding mucosa. Immediately near this, there are two other similar, small tumors 1.0 cm. in diameter; and 2.0 cm. in their maximum diameters. From here on down, there are found in addition 25 other small tumors, similar in appearance, location, morphology and color, and varying from 5.0 to 3.5 cm. in their maximum diameters. The last tumor is 45 inches from the ileo-cecal junction. The circumference of the lower end of the ileum is 10.0 cm. All of the above tumors have their maximum distribution and their apparent origin in that portion of bowel that is opposite the mesenteric attachment. While the colon is moderately dilated, there is no evidence of tumor formation here. There are no noteworthy changes in the rectum, bladder or prostate. Including the small ones, there were 61 tumors throughout the small intestine." (See photograph No. 1).

Microscopic examination disclosed a universal similarity of structure in all the tumors. The mucosa at the margins of the tumors seemed frayed, possessing a looseness of structure in part due to edema and also in part to tumor formation with secondary necrosis and infection. The mucosa was found to be undermined, the invasion often extending for a considerable distance in the submucosa. The supportive stroma was scant. The cells were found to be variable in size (anaplasia) with polyhedral peripheries and rather large clear nuclei with single large nucleoli. While considerable hyperchromatism was present, mitoses were not found because of the abundance of intracellular pigment. In most of the tumors, cells were often found in pseudo-acinar arrangement. (See photomicrograph No. 1A). None of the cells showed a tendency to lay down fibrillar processes that could be demonstrated with Van Gieson stains. The abundance of pigment found in these cells as well as the coarseness of granules is best illustrated in photomicrograph No. 2 which also exhibits their character and size. The effect of the latter could be seen in the smaller lymph nodes which had white centers with black circular peripheries, except at the hili, due to retention in the afferent vessels here. (See photomicrograph No. 3). The metastases in the heart were similar.

COMMENT

It is of interest to note that this man in the third decade of life was working and in apparently a good state of health until 9 months prior to his death. His feeling of fatigue, gradual loss of weight, with pain and tenderness in the epigastrium were all undoubt-

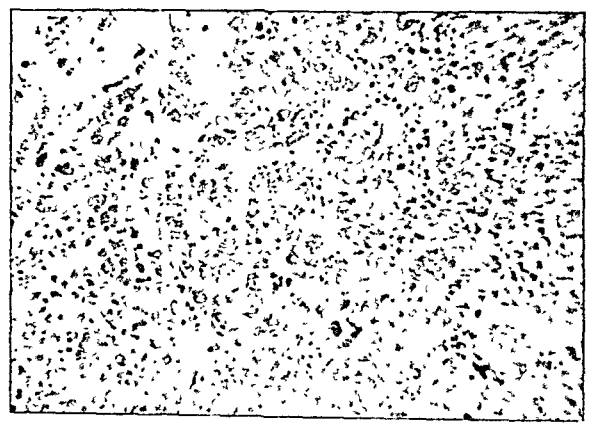


Fig. 2. Autopsy 37-9-36 (H. V.). Photomicrograph No. 1, illustrating the pseudo-glandular character of the growth at A. Note the epithelial character of the cells.

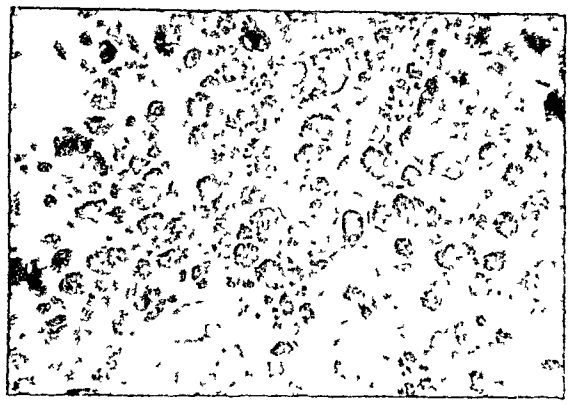


Fig 3 Autopsy 37-9 35 (H. V.). Photomicrograph No. 2, illustrating the pigment-laden cells with epithelial outline of the cytoplasms and a distinctive type of nucleus. Note the abundance of coarse granules of pigment.

edly due to a sluggish digestion, hemorrhage, the absorption of toxic products from the tumors, the excitation of excess peristalsis and the inflammatory reactions which they induced. The oldest tumors were found in the duodenum and upper part of the jejunum. Many of the smaller secondary ones seem to have been implanted at their respective sites. It is also remarkable that there was no evidence of obstruction until late, following the operation, but not due to it, but rather to the bulk of the larger tumors. The absence of free hydrochloric acid in the stomach contents supports the contention that not infrequently there is a lack of this acid in malignant tumors of the intestinal tract, exclusive of stomach involvement. Although permission was not given to examine the brain, there is reason to believe that the symptoms of dementia were secondary to the toxicity from the multiple tumors of the intestine rather than metastases. There is certainly no clinical evidence to lead one to believe that a primary melanoma of the meninges existed. There were found no evidences of a primary tumor other than in the intestines in either the clinical, gross or microscopic studies of this body. The instance here presented is similar to that of Cox and Sloan (3) although the metastases were not as extensive.

While metastatic melanomas of the small intestine are also infrequent (see reports by Maxwell (6), Jones (7), Saphir (8), and others)), the actual instances of the occurrence of such primary tumors here is indeed rare. In addition to the five cases mentioned above, there are references to several others (Lewis (9)). In the case of Cox and Sloan, Wells (H.G.) who performed the autopsy seemed convinced that the melanotic tumor was primary in the jejunum. Likewise Mallory, (F.B.), who passed on the instance reported by Lund, reluctantly regarded it as a primary intestinal tumor, stating that while he had never seen one here, there seemed to be no other primary source. While it is true that the great majority of melanomas (70 to 95%) take their origin from the skin (pigmented nevi) or the choroid of the eye, the ectodermal origin of such cells is by no means a settled question in all instances. Ewing (10) cites the theories of the origin of melanomas as follows: (1) *mesoblastic chromatophores* (Ribbert); (2) *epithelial cells and epithelial chromatophores* (Post and others); (3) *nevus cells in the skin* and *mesoblastic chromatophores* in the *choroid and meninges;* (4) from *endothelial cells of blood* and *lymph vessels* or of *nerve trunks;* (5) from *chromatophores, tactile corpuscles* and *nerve cells forming the end apparatus of the cutaneous sensory nerves* (Masson). Foot (11) subscribed to the views of Masson after a silver impregnation study of nevi. It was his opinion that these cells are derived from the sheath of Schwann. While the latter seems more consistent with our knowledge of pigment distribution and function in animals and man, and while, as Ewing pointed out, it is in harmony with the clinical manifestations, yet the constantly varying character of the cells, which has led us to use the terms "melanoma," "melanosarcoma" and "melanocarcinoma," makes us hold somewhat tenaciously to the type chromatophore, independent of sensory end-organs, in explaining the occurrence of such primary *melanin-bearing tumors as may be found in various* parts of the alimentary tract, other than in the pharynx and the lower end of the rectum. In the instance here reported, the large size of the upper tumors, the progressive diminution in size of the lower ones, as well as the insidious onset, seem to us to point to a primary neoplasia in this part of the intestine. While it is true of melanomas that the primary lesion may be small and the metastases huge, usually there is either a definite history of a previous removal of a primary growth or the evidence of such a lesion at the time of autopsy, none of which were traceable in this case.

SUMMARY

Multiple primary melanotic tumors (64 carcinomas (?)) of the small intestine were found in a man 35 years of age with the development of symptoms 9 months before death. Metastases occurred in the intestine, mesenteric lymph nodes and the heart. There being no other clinically or pathologically demonstrable primary source, it is assumed that the tumor started here from a possible mesoblastic type chromatophore.

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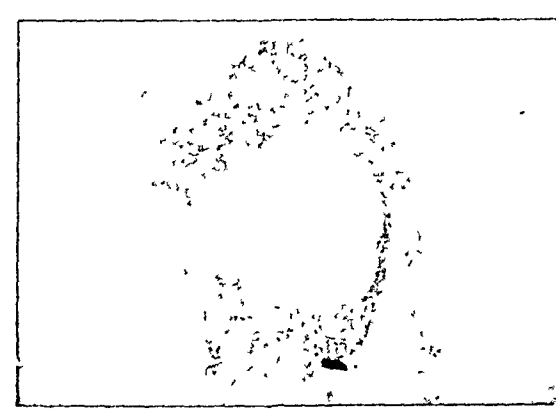


Fig. 4. Autopsy 37-9-35 (H. V.). Low magnification photomicrograph No. 3, illustrating the manner in which the large pigment-laden cells were caught up in the periphery of the lymph node in metastasizing.

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Beriberi Due to a Reducing Diet*

By

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UNUSUAL interest in the *rôle* the vitamins play in health and disease has been exhibited in recent years. Although much has been said about the commoner deficiency diseases, little recognition has been given to deficiency states resulting from a lack of the vitamin "B" accessory food factor.

Up until the time when Strauss (1), in 1935, showed alcoholic neuritis to be directly due to a vitamin "B" deficiency, true "B" avitaminosis, or beriberi was considered of comparatively rare occurrence in the United States. Following is the report of such a case, a patient who suddenly developed generalized edema, *following a prolonged reducing diet, deficient in* vitamin "B."

REPORT OF CASE

The patient, a lawyer, aged 27, was seen first in the Cleveland Clinic, on February 6, 1932. Medical advice was sought because of sudden increase in weight, accompanied by swelling of the face and legs. The illness had begun one week before admission when the patient first had noticed a swelling of his abdomen and legs which had appeared rather suddenly. The patient found that he had gained eleven pounds in weight over a period of three days; at the end of a week he had gained sixteen pounds. The swelling increased in proportion to the increasing weight, and always was worse in the mornings, tending to decrease towards mid-day. On several occasions the patient had awakened in the morning with his eyes swollen completely shut. His only other complaints were of a feeling of discomfort in the lower chest and upper abdominal region, of some weakness and of loss of "pep." There were no genito-urinary symptoms until about two days before his admission when he had noted some frequency and since then had been voiding an unusually large quantity of urine.

On questioning the patient it was found that he had been on a very restricted, poorly balanced diet for the last year and a half. In January, 1930, numerous furuncles, scattered over his entire body had developed. These had proved very resistant to treatment and his physician finally had advised a diet in which starches, sugars and fruits were prohibited. The patient had existed on a grapefruit and a small portion of meat (beef) each day with a little lettuce once or twice a week. After dieting in this manner for about six weeks, the boils had disappeared and the patient had lost about 25 pounds in weight. He felt so much better with his weight reduced, that he decided to continue on this diet, which he carried out with very little variance for a total period of a year and a half. After dieting for a few months, he soon lost his appetite and had no desire for food. During the entire period his weight had been reduced from 165 pounds to 105 pounds. His weight was maintained for three to four months at 105 to 110 pounds, when edema supervened.

When seen by us, the patient weighed 127 pounds and his height was five feet, three inches. The skin and mucous membranes appeared healthy. The eye examination revealed nothing abnormal; the tonsils had been removed and there was no evidence of oral sepsis. The thyroid was not enlarged and there were no palpable glands in the neck. There was a general puffy appearance of the face, most marked in the tissues around the eyes. The chest was symmetrical, the lungs clear, and no pleural effusion could be demonstrated. The heart seemed normal in size and no murmurs or arhythmia could be demonstrated. The skin over the pectoral region was very loose and edematous; palpation showed the existence of pockets of fluid between the skin of the chest wall and the underlying subcutaneous tissues. There was diffuse edema of the abdominal wall similar to that found in the chest. There was no evidence of ascites. The external genitalia were entirely normal, without any evidence of edema. The legs, ankles and feet showed a moderate amount of edema which pitted deeply on pressure. All superficial and deep reflexes were normal. There was no evidence of arteriosclerosis. No muscular atrophy or weakness could be demonstrated; there were no sensory disturbances, and the Jongkok test was negative.

The pulse rate was 60 and the blood pressure was 100 systolic, 64 diastolic. The blood count showed 4,400,000 erythrocytes, 7,250 leucocytes, and the hemoglobin, 84 per cent. The blood sugar was 77 milligrams per hundred cubic centimeters one hour after a meal. The level of the urea in the blood was 24 milligrams per cent. The results of the urinalysis were negative except for a low specific gravity, 1.010. The Wassermann and Kahn tests were negative. Roentgenographic studies of the gastro-intestinal tract revealed pylorospasm and a very large, atonic colon.

COMMENT

The information obtained from the physical examination and from the routine laboratory tests was sufficient to rule out the presence of any of the diseases commonly producing edema. The history of a low caloric intake over a long period of time, which had

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Submitted June 8, 1936.

resulted in marked loss of weight, anorexia and weakness followed by the rather sudden onset of edema, immediately raised the question as to whether or not this might be a case of so-called inanition edema. It was felt that the condition might easily be a vitamin "B" deficiency disease, that is, a "wet form" of beriberi in which the neuritic symptoms were absent or masked by the edema.

The rather unusual features of the case prompted further studies. The plasma protein, carbon-dioxide-combining power of the plasma, and the inorganic constituents of the blood were checked with the following results:

Serum Proteins	6.74	per cent
Serum Albumin	3.97	per cent
Serum Globulin	2.77	per cent
Cholesterol	150	mg.
Sodium Chloride	577	mg.
Phosphorus	3.5	mg.
Calcium	9.7	mg.
Urea	24.0	mg.
Uric Acid	1.7	mg.
Non-Protein Nitrogen	22.4	
Carbon Dioxide Combining Power	57.6	
Basal Metabolic Rate:		
Dubois	—23	per cent
Sanborn	—26	per cent
(Based on 116½ pounds)		
Phenolsulphonephthalein:		
First hour	30	per cent
Second hour	35	per cent
Urea Clearance	67	per cent

Comment. The plasma proteins in which we were most interested, were entirely within normal limits as were the carbon-dioxide-combining power of plasma and the inorganic constituents of the blood. The basal metabolic rate was rather low but this is to be expected in patients with edema. The edema in this case could not be explained on the bases of low osmotic pressure of serum proteins, as is found in inanition edema; and hence it was felt that it must be closely related, if not identical, with the edemas which occur in the wet types of beriberi. Although there were no neuritic symptoms in this case, it has been repeatedly shown that "ship" beriberi, a wet form of the disease, is a deficiency disease in which nervous phenomena are rarely present and that edema of various degrees is the predominating, oftentimes the only, physical finding.

COURSE

The patient, thoroughly alarmed about his condition, was quite willing to co-operate, and to dispense with his past dietary regimen. He was given a diet with a high vitamin, and low carbohydrate content, with a supplementary supply of vitamin "B" in the form of a concentrated vitamin "B" extract.

His response to this form of treatment was most satisfactory. The edema disappeared rapidly. In a weak he had lost ten pounds, his appetite had returned to normal, and he felt indeed much improved. The edema had entirely disappeared from his face, but was still evident in the pectoral region and in the lower extremities. He was advised to continue the treatment and to return at weekly intervals for observation. Edema continued to decrease and there was a gradual loss in weight, so that at the end of three weeks, there was no evidence of any gross edema. He had lost 16 pounds, undoubtedly due to the loss of fluid, in fact the amount of fluid lost was probably even greater than would appear from the figures, as most likely he had gained actually on the more substantial diet. The patient then began to gain, hoping to reach and maintain his weight at a level between 125 and 130 pounds, the proper amount for a man of his stature. Simultaneously with the disappearance of the edema there was a very marked increase in the urinary output.

In June, 1932, after having been free from symptoms for four months, the patient returned because of a reappearance of the edema. He had gained ten pounds rather suddenly and had had a very scanty output of urine. These symptoms occurred while the patient was on a three weeks' business trip, during which time he had stopped taking the vitamin "B" extract. The edema appeared almost two weeks after the extract was discontinued. An analysis of the serum proteins was done at this time and was found to be entirely normal. (Serum proteins, 8.32; albumin, 4.74; globulin, 3.58). Curiously enough, ten days after treatment with vitamin "B" was reinstated, the edema had entirely disappeared and the urinary output had returned to normal. The patient has remained well to the present time; however, he still is taking a liberal supply of vitamin "B" daily along with the proper diet. Subsequent examinations failed to show any evidence of peripheral neuritis. Repeated urine analyses during the period of observation showed no evidence of renal damage.

With the marked amelioration of symptoms and entire disappearance of edema on a high vitamin "B" diet, without the aid of other therapeutic measures, it was felt that this case was indeed one presenting the clinical picture and course of wet beriberi.

DISCUSSION

Although vitamin "B" is quite widespread in the animal and vegetable kingdom, we know that beef, lettuce, and fruit juices, which constituted this patient's diet, contain relatively small amounts of it, and when the diet is otherwise deficient, large amounts of these foods must be consumed in order to prevent the development of a deficiency disease. Vedder (7), in an excellent monograph on this subject stated that experimental work on beriberi, has demonstrated that the body is unable to store up much reserve vitamin. The depletion period as shown by various human feeding experiments may occur in man within 7 to 120 days. In the patient under discussion there were no symptoms for about a year and a half; the patient apparently feeling perfectly well until the sudden onset of edema and weakness caused him to seek medical advice.

The cause of edema in beriberi always has been obscure. McCollum (2) expresses the opinion that protein shortage is the probable cause of starvation dropsy and that wet beriberi may be an expression of two specific dietary lacks, protein starvation and deficiency of vitamin "B." With the discovery that plasma proteins are reduced in cases of nephrosis and other edemas it was thought that some light might be thrown on the mechanism of the production of edema in beriberi. However, no confirmatory reports are to be found in the literature. Kabayaski (3) reported the serum proteins normal in beriberi while Shigeari (4) and associates observed low values during the

edematous stages which rose to normal or above after the disappearance of the edema.

Nakazama (5) and co-workers reported a serum albumen values seldom below 4 per cent and colloid osmotic pressure of only one per cent below normal. They found the molecular weight of albumen greater in the edematous forms and suggest the hypothesis that the blood building mechanism is disturbed in beriberi. McCarrison (6) found that the adrenals of fowls suffering from "B" avitaminosis are considerably enlarged, and that the secretion of adrenalin by these enlarged glands is proportionally increased. He suggested that the edema may be due to circulatory changes resulting from this increased secretion of adrenalin. Vedder (7) stated that there is considerable experimental evidence to indicate that two vitamins are deficient in the diet that produces beriberi and suggested the possibility that the deficiency of one, the anti-neuritic vitamin, produces degeneration of the nervous system and the symptoms of dry beriberi, while deficiency of the second vitamin produces generalized edema and the syndrome, wet beriberi. Sargent (8) pointed out that in the wet form of beriberi an affection of the vasomotor nerves produces edema while in the dry form paraplegic manifestations are produced and palsy and atrophy of muscles occur.

The instance cited illustrates well one of the dangers encountered in the use of "reducing diets" without proper medical supervision.

SUMMARY

A young man exhibited generalized edema and weakness following a generally inadequate diet, deficient in vitamin "B." Laboratory tests, including a study of the plasma proteins and of the inorganic constituents of the blood were entirely normal. The complete disappearance of the edema and general symptoms, after a course of treatment consisting of the administration of vitamin "B" and an adequate diet, is proof that the condition was a deficiency disease, a "B" avitaminosis or wet beriberi.

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ABSTRACTS

EXPERIMENTAL PHYSIOLOGY

COLP, R.

Biliary Duodenal Intubation. S. G. O., Vol. 62, No. 2, pp. 157-163, Aug., 1936.

In the author's opinion biliary duodenal intubation is a valuable procedure which should be applied in a greater variety of conditions. In addition to its use in cases of stricture or division of an extrahepatic bile duct he recommends it in any case in which external biliary drainage is undesirable, or one in which internal biliary drainage is imperative.

Many persons become markedly debiliated from prolonged loss of bile.

Another indication for biliary duodenal intubation is in the treatment of choledochal cysts. It seems questionable whether this procedure is preferable in cases of stricture near the porta hepatis in which the distal segment of the duct cannot be found. The author feels that it is perhaps better to transplant a firm fistulous tract into the stomach or duodenum.

In selecting the tube to be used the author recommends the best grade of rubber tubing, which, at the same time, is radiopaque. While a soft and pliable tube is essential it must be sufficiently rigid to maintain its lumen against external pressure in spite of ample fenestration. The tube should be large enough to fill the choledochus and fit snugly within the narrowed and spastic area of the papilla. It should be introduced from 8 to 10 centimeters down the duodenum and left so or anchored with a silk suture.

Five figures and four case reports accompany the article.

Nelson M. Percy, Chicago.

MOON, VIRGIL H., AND MORGAN, DAVID R.

Experimental Pulmonary Edema. Arch. Path., 21:5, p. 565, May, 1936.

The authors have studied experimentally pulmonary edema in dogs the result of (1) muscle implanted in the peritoneal cavity, (2) burns, (3) intestinal obstruction, (4) the intravenous injection of bile and of sodium glycocholate, (5) sodium phenobarbital, and (6) histamine. The type of edema produced in the lungs by each of the above intoxicants was characterized by a protein content approximating that of the blood plasma and a high specific gravity. This is in contrast to the edema occurring in nephrosis or dietary deficiencies which has a low protein content and a low specific gravity.

The above form of pulmonary edema results from increased vascular permeability and is accompanied with hemoconcentration (as much as 30 per cent increase, in some instances, of red blood cells per cmm. and grams of hemoglobin per 100 c.c. of blood) and with circulatory inefficiency. The mechanism of such edema is integral with that of the shock syndrome. The degree of edema found is less when a fatal shock develops rapidly, but when a few days elapse before death occurs it is found to be extensive and a common type of terminal pneumonia is found with it.

The acute congestion which precedes this type of edema as an accompaniment of shock resembles in appearance passive congestion. Its differentintion from the latter is to be discussed in a subsequent report.

N. W. Jones, Portland, Oregon.

GAITHER, ERNEST H.

Recent Advances in Gastro-enterology: Chairman's Address. J. A. M. A., Vol. 107, pp. 549-552, Aug., 1936.

One of the most stimulating recent publications is the monograph by Faber, in which he clearly sets forth his own views and those of other eminent authorities as to proofs of the presence and frequency of both acute and chronic gastritis. He has tried to show the relationship of acute and chronic gastritis to superficial and deep ulcerations; chronic gastritis and its tendency to

precede ulcer and carcinoma; and the relationship which hyperacidity and anacidity bear to these conditions.

Bloomfield and Polland published a monograph termed "Gastric Anacidity" which reports their research work on the secretory function of the stomach.

Castle's demonstration of the etiology of pernicious anemia is undoubtedly one of the most brilliant contributions of recent years. Hollander has also done some work concerning the composition of gastric juice.

Greengard, Maison and Ivy have isolated a substance known as enterogastrone, which inhibits gastric secretion and motility in the dog. Dragstedt has written an article on acute dilatation of the stomach which is valuable to internist as well as surgeon. Rehfuss has written "Medical Treatment of Gall Bladder Disease" while Lyon has done valuable work on gall bladder drainage.

The flexible gastroscope has been introduced and is expected to greatly increase the knowledge of gastric pathology in a few years.

Clasen and Eusterman have recently published some very excellent work on syphilis of the stomach.

Gastro-intestinal pain has been ably dealt with as regards localization, genesis, and probable pathways, by such men as Christensen, Boyden, Rigler and Rivers. Rowe, Duke and Vaughan have made splendid progress in allergic manifestations and gastro-intestinal disease.

The etiology of gastric ulcer is still in the theoretical stage, while Sippy and Smithies have done much in the treatment of the condition. Sara Jordan has done excellent work in the treatment of peptic ulcer.

Miller and Gray have done work on the intubation of the small intestine and have studied the influence of organic and inorganic acids on the motility of the small intestine.

Crohn presents a splendid piece of work, "Regional Ileitis" claiming the discovery of a new disease entity. Felsen claims that this condition and *chronic idiopathic ulcerative colitis are* the end results of bacillary dysentery. Barren claims that ulcerative colitis is due to a specific organism and reports successful treatment with vaccines and serum. Sullivan has also studied the psychogenic factor related to ulcerative colitis.

Ivy has isolated cholecystokinin, a substance which has a specific action on the gall bladder. The function of the liver may be studied by such tests as the van den Bergh, coagulation time, sedimentation, galactose tolerance, bronisulfalein, rose bengal, Takata-Ara, and the hippuric acid test.

The Enzyme Committee of the American Gastro-enterological Association presented various reliable methods for the study of enzymatic activity. They came to various conclusions, too numerous to enumerate in this brief review.

The effect of a diet rich in carbohydrate has been shown by L. R. Brown to bear some relation to the etiology of migraine.

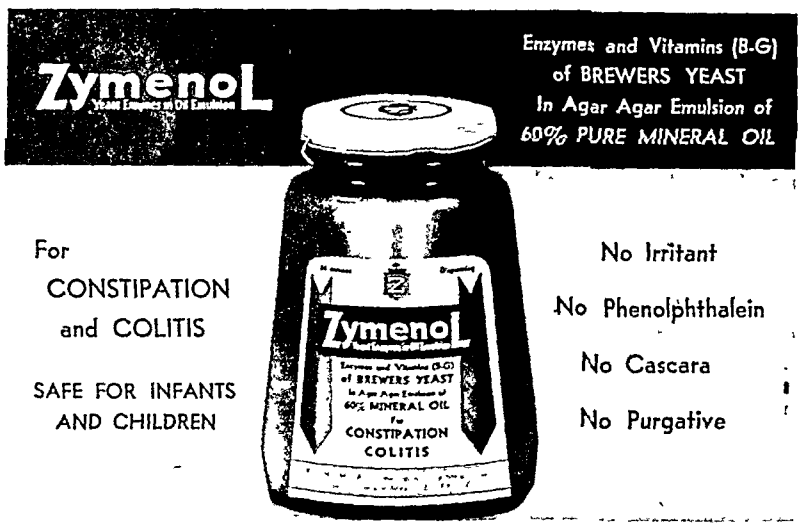
Dr. Madge T. Macklin has emphasized and demonstrated the importance of hereditary factors in gastro-intestinal disease.

Many advances have been made in radiologic diagnosis of gastro-intestinal disease, among the most important of which is Kantor's "Colon Studies" and Schotzki's work on the diagnosis of small ulcerative lesions and the gastritides. Cholecystography has also been greatly improved by the use of an oral dye. Excellent work has also been done in anomalies of the esophagus, especially the congenitally short type.

Francis D. Murphy, Milwaukee.

BLANKENSTEIN, M. A., AND RICHARDS, C. E.
Garlic Breath Odor. J. A. M. A., Vol. 107, pp. 409-410, Aug. 8, 1936.

The fetid odor that persists for many hours on the breath of one who has eaten garlic or onions has been thought to be due to substances which pass into the blood stream during digestion.



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Recently work was published which indicated that the odor might arise from particles of onion or garlic retained in the structures of the mouth.

Because of the controversy caused by the aforementioned theories, the following experiments were carried out. Garlic in one form or another was fed to three patients, one who had a gastrostomy fistula because of a carcinoma of the esophagus; another who had a tracheotomy fistula because of a cancer of the larynx; and the third, a boy who had a tracheal fistula because of a stricture of the larynx. In all of these cases the odor of garlic appeared on the breath, and in none of the cases was it due to the particles left in the mouth. When chloramine was given as a mouth wash, the odor disappeared for only thirty to sixty minutes. From the above results, the conclusion was reached that garlic breath odor is due to substances carried in the blood.

Francis D. Murphy, Milwaukee.

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Restricted diets indicated in intestinal ulcers, diabetes, obesity, kidney, liver, gastric and many other disturbances, often contribute to the onset of deficiency diseases because of the limited intake of food. Complications develop in these cases which may be more serious than the original ailment.

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SCHIODT, E.

Blood Regeneration in Patients with Hematemesis or Melana from Peptic Ulcer, Treated with the Usual Ulcer Cure and with the Menlengracht Treatment. Amer. Jour. Med. Sci., p. 163-167, Aug., 1936.

In July, 1931, Melengracht altered the treatment of patients with hematemesis or melena in this department. Previously such patients were given the usual "ulcer cure." Instead of waiting about four weeks for the establishment of the "puree diet," he gave it from the first day of admission, which often meant the first day of bleeding. This is a well balanced diet which includes meat, fish and vegetables, fruit, potatoes, in fact all sorts of food, finely minced in the form of force meat, mashed potatoes, pureed vegetables, fruit soups, jellies and so on. Lactate of iron and an aperient such as cascara were also given. A careful comparison study was made of 10 patients on the old "ulcer cure" and 10 patients on puree diet and iron. The patients on "ulcer cure" regenerated both red blood cells and hemoglobin much more slowly and less completely than did those on the puree diet and iron. In the latter cases the red blood cells and hemoglobin rose more nearly together, the color index being higher about 1., than in the ulcer cure group. The cases starting with r.b.c. 2.5 million and hgb. 50% on a puree diet with iron showed a rise in 30 days to 4 million red blood cells and 80% of hemoglobin, whereas, those on ulcer cure, with the same start reached only about 3.2 million r.b.c. and hemoglobin 55% in 30 days; a low color index all the way. The patients on the more abundant diet felt subjectively better and their clinical improvement was obvious to both doctors and nurses.

Allen Jones, Buffalo.

SYDENSTRICKER, V. P., ARMSTRONG, E. S., DERRICK, C. J., AND KEMP, P. S.

On the Existence of an Intrinsic Deficiency in Pellagra. Am. Jour. Med. Sciences, p. 1-9, July, 1936.

Method. Five patients were maintained on the original Goldberger-Wheeler pellagra-producing diet to which was added 25. gm. of fat salt pork. Gastric juice was obtained from normal medical students and from patients with no gastro-intestinal disease. To obviate the probability of increased gastric digestion of food, all doses of gastric juice were administered in the evening some 4 hours after the evening meal.

After reporting 6 cases in detail the authors suggest that there is an intrinsic factor present in normal gastric juice which makes possible the utilization of minimal amounts of extrinsic factor. (B2). Prolonged remission in two instances indicates that this intrinsic factor may be stored in the body. The hypothesis is advanced that in

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COMMUNICABLE DISEASES

Disease	*Incubation Period* (average)	*Isolation Period* (average)
Chicken Pox	12-16 Days	3-14 Days
Diphtheria	2-4 Days	After 12th Day—until cultures negative
Epidemic Meningitis	1st Week	Until cultures negative
Measles	2nd Week	Until 5 days from onset rash
Mumps	3rd Week	Duration of Swelling
Poliomyelitis	3-10 Days	21 Days
Rubella	3rd Week	Duration of catarrh and rash
Scarlet Fever	1st Week	After 21st Day—until cultures negative
Whooping Cough	2nd Week	Until 4 weeks from onset whoop

From American Journal of Public Health—March, 1927

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pellagra there is an intrinsic deficiency of variable degree. Some retain enough to recover on diets grossly deficient in Vitamin B_2; others regenerate it in the presence of an abundance of the extrinsic factor while some are totally lacking in it but may recover under substitution therapy or die of nervous or cardiac damage inflicted before therapy was started. Further, the intrinsic factor is exhausted or cannot be regenerated during prolonged deprivation of extrinsic factor.

Allen Jones, Buffalo.

ROENTGENOLOGY

JENKINSON, E. L.
Cholecystography. J. A. M. A., Vol. 107, pp. 755-757, Sept. 5, 1936.

Cholecystography, as brought forth by Graham, Cole and their co-workers, is quite generally accepted in determining whether or not the gall bladder is functioning normally. When done under the proper conditions, namely cooperation and control of the patient, there is practically no diagnostic procedure more accurate.

The patient should not be allowed to take any fatty food from the time of the ingestion of the dye until the films are obtained. The patient should also be instructed not to move during the exposure. Slight movement may frequently obliterate a normal gall bladder shadow.

Cholecystograms were made on ninety-five patients; forty-nine were females and forty-six were males. The average age was forty-two years, and all had gall bladder symptoms. Seventy of these were normal, twenty-two were pathological and three patients failed to retain the dye.

Of the twenty patients with a pathological response, eight or forty per cent showed a normal response after being treated medically with a high fat diet and dehydrochloric acid; two showed a normal response with stones in the gall bladder, and four showed a poor response with stones in the gall bladder; five showed no response on two or more occasions; one showed a normal response followed by nonfilling; and two showed variable responses.

From these results the conclusion was reached that operative intervention is not indicated unless one or more negative responses occur after medical treatment.

Francis D. Murphy, Milwaukee.

COLLINS, E. M., AND ROOT, J. C.
Elimination of Confusing Gas Shadows During Cholecystography. J. A. M. A., Vol. 107, No. 1, pp. 32-33, July 4, 1936.

Cholecystographic interpretation is most frequently confused by the presence of gas in the right side of the gastro-intestinal tract. Enemata have been tried as a means of abolishing this condition, but results have been poor. Because of this, pitressin has been tried in doses of one ampoule (10 pressor units) in those cases in which confusing shadows appeared in the right side of the abdomen. Additional cholecystograms are taken forty-five to sixty minutes after the pitressin has been given. Effective results were obtained in 82 per cent of the seventy-three cases; 75 per cent of the patients had one or more stools within 45 minutes of the injection and almost all the patients had mild, cramp-like abdominal pains. In some of the cases there was a drop in blood pressure, in some no change and in others a moderate rise.

Francis D. Murphy, Milwaukee.

THERAPEUTICS

STEIGMANN, FREDERICK, AND SINGER, HARRY A.
Spontaneous Pneumothorax Simulating Acute Abdominal Affections. Am. Jour. Med. Sciences, July, 1936.

Among the abdominal symptoms of thoracic disease, those of lobar pneu-



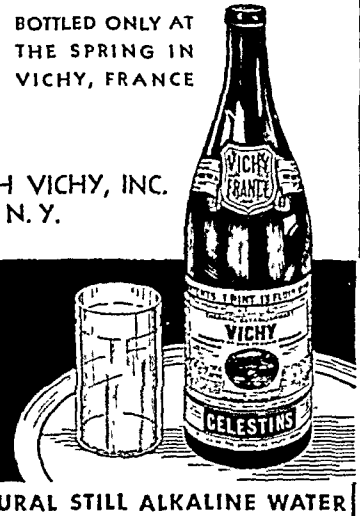
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VITAMIN UNITS AND STANDARDS

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Believing that these units and the standards upon which they are based would be of interest to our readers, they have been tabulated and defined below (1):

Vitamin A

The reference standard is a solution of pure beta-carotene in an inert oil, of such concentration that one gram of solution contains 300 micrograms (0.300 mg.) of beta-carotene. The International Unit, or I.U., of vitamin A is the vitamin A activity of 2 mg. of this standard solution, or 0.6 micrograms of beta-carotene.

Vitamin B1

The reference standard is the concentrate produced from rice polishings, by a specified adsorption method, in the Medical Laboratory of Batavia (Java). The International Unit for vitamin B1 is the vitamin B1 activity of 10 mg. of this standard adsorption product.

Vitamin C

The standard of reference for vitamin C is a specified sample of pure levo-cevitamic acid (levo-ascorbic acid). The International Unit for vitamin C is the vitamin C activity of 0.05 mg. of this standard.

Vitamin D

The reference standard for vitamin D is a solution of irradiated ergosterol, prepared under specified conditions at the National Institute for Medical Research (London). The International Unit for vitamin D is the vitamin D activity of 1.0 mg. of this standard solution.

These International Units for expressing vitamin contents have been specified in the most recent Pharmacopoeia of the United States (2) as well as by the Council on Pharmacy and Chemistry (3) and the Council on Foods of the American Medical Association (3), and provision has been made for distribution of the standards in this country (4).

These units have been used to express vitamin potencies in recent studies on canned foods, the results of which further emphasize the fact that these foods rank among the most important sources of the vitamins essential in human nutrition (5), (6), (7).

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1, 1935 [illegible]

2, 1936 Pharmacopoeia of the United States of America, Revised Ed. [illegible] p. 291

3, 1935 Report of the Council, J. Am. Med. Assn. IX, 1935

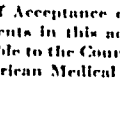
4, 1935 J. Am. Pharmaceutical Ass. Chem. 15, 611

5, 1935 J. Home Econ. 27, 658

6, 1936 Food Research 1, 223

7, 1935 J. Nutrition 2, 69

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monia, acute fibrinous pleuritis, coronary thrombosis, acute fibrinous pericarditis closely resemble, at times, the "acute surgical abdomen." Disease of the abdominal structures may be simulated by osteomyelitis of the thoracic vertebrae, intercostal neuralgia, etc. Acute cardiac decompensation with sudden hepatic engorgement, ruptured or dissecting thoracic aneurism, pulmonary infarct, acute mediastinitis and spontaneous rupture of the oesophagus may mimic primary abdominal disease. The authors found only four reports of spontaneous pneumothoracic simulating primary abdominal disease in the medical periodical literature. The authors observed three cases and attribute their detection to frequent resort to the Roentgen ray in questionable abdominal conditions. The cases found in the literature are described and then author's cases. In comment, attention is directed to the difficulty of diagnosis because intense abdominal pain, nausea and vomiting, associated with tenderness and rigidity which were present in the cases recorded, constitute a syndrome which generally demands immediate laparotomy. The error of regarding a sudden pneumothorax as an abdominal lesion can almost invariably be avoided, the authors write, by a careful chest examination of each patient with an atypical picture of abdominal disease. The Roentgen ray is of extreme importance. A small amount of free air is difficult to identify unless fluid is simultaneously present in the chest cavity. Sudden pneumothorax simulates ruptured peptic ulcer so Roentgen ray serves a double purpose.

Many years ago I read a paper at a meeting of the American Medical Association entitled "Abdominal Symptoms of Thoracic Disease" so this valuable contribution by the above authors interests me very much.

Allen Jones, Buffalo.

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BRODY, HENRY, AND SMITH, L. W.

The Visceral Pathology in Scarlet Fever and Related Streptococcus Infections. Am. Jour. of Path., 12:3, p. 373, May, 1936.

The authors present a study of the visceral pathology in scarlet fever and related streptococcus infections. It is based upon the histological examination of material from 44 frank cases and 15 presumptive cases of scarlet fever. They believe the underlying lesion is one of vascular injury with a concurrent, perivascular round cell infiltration. These lesions were found widespread throughout the visceral organs, particularly constant in the hearts, livers, kidneys, adrenals and spleens of these cases. They believed the lesions were probably due to a circulating toxin, for in no instance were they able to demonstrate microorganisms in stained sections. In most of the cases hemolytic streptococci were obtained in blood and tissue cultures. The interstitial mononuclear lesion is not considered specific for scarlet fever. It is seen in other infectious diseases when associated with streptococcic infections, notably diphtheria and measles, although less widely disseminated and less frequently found than in scarlet fever. Its frequency in many organs in scarlet fever, however, and the similarity of its appearance in the various organs, suggest the fundamental importance of the lesion in the pathology of this disease.

N. W. Jones, Portland, Oregon.

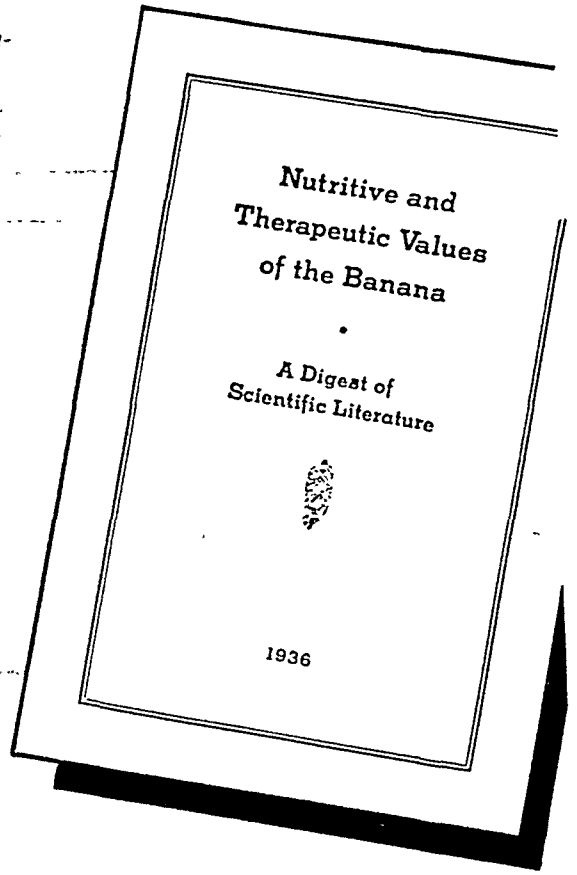
STRAUSS, ALFRED A., STRAUSS, SIEGFRIED F., AND STRAUSS, HERMAN A.

A New Method and End-Results in the Treatment of Carcinoma of the Stomach and Rectum by Surgical Diathermy (Electrical Coagulation). South. Surg., 5:348-359, October, 1936.

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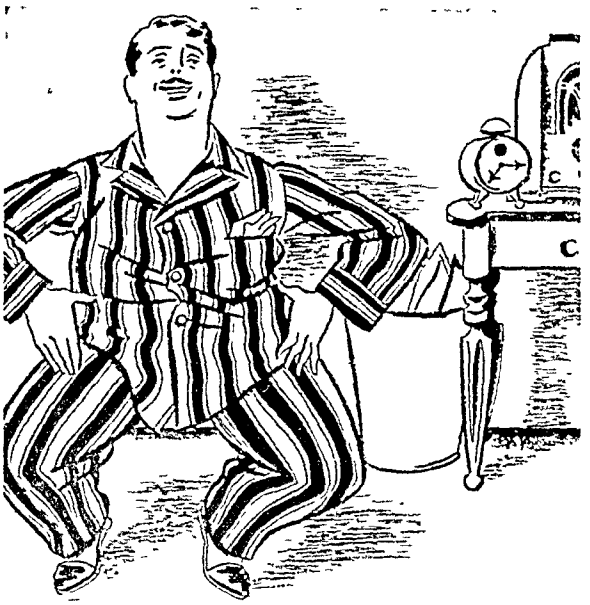
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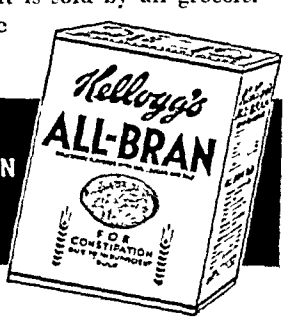
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cases had preliminary colostomy established. All three stomach cases had a jejunostomy done for the purpose of feeding during the course of the treatment. The rectal growths were accessible through a proctoscope. Since the stomach must be kept open for an interval of three to six weeks to allow the proper time interval between the two or three necessary treatments temporary closure is obtained by the use of a zipper or a rubber patch.

The progress of the pathological lesion in its response to this type of treatment is described in some detail. There is first excavation, then appearance of edematous jelly-like tissue, absorption of this tissue, and connective tissue formation with occasional contraction but usually softening of the tissue. The excellent results reported are attributed by the authors not only to the simple mechanical destruction of the cancerous tissue but also to the liberation of certain substances which are absorbed in the body in general. These substances are believed to stimulate the reticulo-endothelial tissues and macrophages which not only prevent further growth but also help to destroy the growth present. These effects seem applicable to the regional lymph nodes and probably the liver as well.

It is interesting to speculate upon the possibilities suggested by this type of treatment and the reaction obtained in malignant cells.

J. Duffy Hancock, Louisville.

ABDOMINAL SURGERY

PRIESTLEY, J. T., AND MCCORMACK, C. J.

Generalized Peritonitis Secondary to Rupture of the Appendix. With Special Reference to Serum Therapy. S. G. O., Vol. 63, No. 5, pp. 675-680.

In the treatment of acute appendicitis the authors prefer the Ochsner type of treatment for those cases with generalized peritonitis. Immediate operation is favored in all cases in which rupture has not occurred, and in certain cases in which rupture has occurred. If rupture has occurred recently, and peritonitis is not advanced, operation is performed, but extreme care must be taken to prevent spreading the infection. If rupture occurred remotely, and the process seems to be held in check by the patient's natural defense mechanism, operation may be deferred until localization is completed. Operation may be advisable if a local peritonitis tends to become generalized while under medical management. If operation is performed in the presence of peritonitis, drainage should be instituted, and appendectomy may or may not be performed. If the appendix may be removed without traumatizing the already inflamed structures it should be done, but if it is not readily accessible it should be left in place and removed at a later date.

Routine bacteriologic studies in cases of appendicitis reveal a great variety of organisms. Most commonly aerobic cultures yield Escherichia coli and others, while anaerobic cultures yield Clostridium welchii and others. The theory has been advanced that the anaerobic organisms create a more favorable environment for the growth of streptococci and other aerobic organisms which are commonly considered to be the lethal organisms in peritonitis.

On the basis of those observations Weinberg has prepared three serums to be used as an adjunct to the surgical or medical treatment of acute appendicitis with peritonitis. The first is a polyvalent serum for the anaerobes commonly found in these cases. The second is a colon bacillus serum, while the third is a serum to combat any other organisms present.

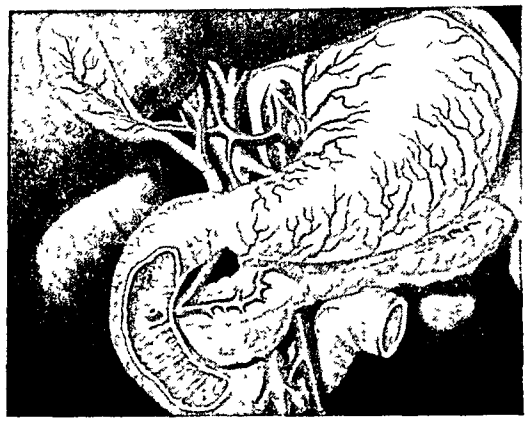
The authors have used these sera in a number of cases, and are of the opinion that the method offers some hope of reducing the mortality of peritonitis secondary to rupture of the inflamed appendix. Certain of their patients, they believe, have been benefited materially from this serotherapy.

They recommend adequate doses given preferably within 24 hours of the onset of peritonitis. It is of value in more

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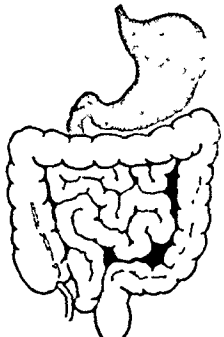
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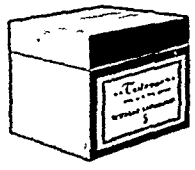


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advanced cases also. They use 40 cubic centimeters of the polyvalent anaerobic serum, and 30 cubic centimeters of each of the other two, as an initial dose, and subsequent amounts as indicated.

Three tables and a bibliography accompany the article.

Nelson M. Percy, Chicago.

STEINBERG, M. E.

The Surgical Treatment of Deep Seated Non-Resectable Ulcers of the Duodenum. S. G. O., Vol. 63, No. 5, pp. 625-631, Nov., 1936.

The author describes a new method of surgical treatment of deep seated ulcers of the duodenum. Proper and successful application of the method depends upon a thorough understanding of the principles involved and the technic employed. In certain cases in which anatomical anomalies or changes resultant from old inflammatory processes make the application of this method unsafe, the modified Finsterer exclusion operation may be performed.

In the author's technic the stomach is divided three finger breadths proximal to the pylorus and the proximal portion reflected to the left out of the way. Through the pylorus the duodenum is palpated, the ulcer located and its size determined. The anterior wall of the duodenum is now incised transversely along a line just proximal to the proximal border of the ulcer and reflected distally. A flap of the anterior duodenal wall sufficiently large to invert and cover the entire ulcer must be obtained; if this is not possible without tension, the duodenum would be closed and the modified Finsterer operation performed. The ulcer is now cauterized with phenol and alcohol, and the mucosa removed from its edges by means of a small currette. The free margin of the anterior duodenal wall is now sutured to the distal margin of the ulcer. Another row of sutures is now placed through the proximal margin of the ulcer and the serosa of the anterior duodenal wall inverted over the ulcer. The ulcer is thereby covered. The posterior duodenal wall and a portion of the posterior wall of the stomach from which the mucosa has been removed is now reflected over the closed duodenum and sutured in place. Finally the capsule of the pancreas is sutured to the closed end of the duodenum.

The author has used this method in three cases and recommends it because it precludes any injury to the common duct, pancreatic ducts, pancreas, or the blood supply of any of the structures involved.

Eight figures and a bibliography accompany the article.

Nelson M. Percy, Chicago.

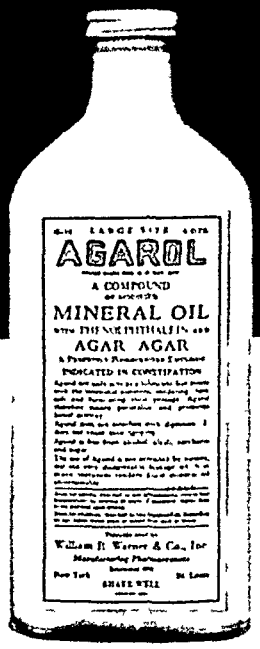
BRUNN, H.

Acute Pelvic Appendicitis. S. G. O., Vol. 63, No. 5, pp. 583-592, Nov., 1936.

In an attempt to bring forcibly to the minds of the profession a certain form of atypical appendicitis in which the appendix is placed either on the brim of the pelvis, or deep in the pelvis, the author reports in detail several such cases and discusses some of the diseases which are most likely to be mistaken for it.

The most constant symptom is pain which, at the onset, does not differ particularly from that of any appendiceal attack. When localization takes place, it is more frequently on the left side than the right side in this type of appendicitis. Vomiting may or may not occur. Diarrhea may accompany the onset. Physical findings are atypical of appendicitis; there may be no tenderness even on deep palpation and no rigidity. The temperature may be normal. Irritation on urination is frequently a symptom which must be brought out on direct questioning. Examination of the urine will frequently show the presence of red blood cells when the appendix lies against the bladder or a ureter. The blood count, which is important, is usually high, 15,000 to 20,000, with a high polymorphonuclear

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count. Rectal examination, properly done and repeated once or twice daily, will reveal tenderness in those cases in which the appendix is low in the pelvis.

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Two tables and some illustrative case reports with individual discussion accompany the article.

Nelson M. Percy, Chicago.

CHRISTOPHER, F.

Intussusception in Adults. S. G. O., Vol. 63, No. 5, pp. 670-674, Nov., 1936.

The author reviews the literature on intussusception in adults and reports two new cases. The etiologic agent most commonly recognized has been a tumor, either benign or malignant. In adults the symptoms are usually those of acute intestinal obstruction, but they may simulate cholecystitis or peptic ulcer.

One case of chronic ileocecal intussusception, and one of high jujunal intussusception due to a papillary adenoma, are reported.

Three figures and a bibliography accompany the article.

Nelson M. Percy, Chicago.

WOLFSON, W. L., AND ROTHENBERG, R. E.

A Simple Method of Amputating Exteriorized Bowel with the Carr Hilar Lobectomy Clamp. S. G. O., Vol. 63, No. 4, Oct., 1936.

In order to avoid the occasional complications following the secnod stage Mikulicz operation, the authors use and recommend the use of the Carr hilar lobectomy clamp. It is applied at the bedside about 36 hours after the operation, and usually falls off, or may be cut away, after 4-5 days. A small incision may be made in the distended bowel and a catheter inserted to allow gas and fecal matter to escape when distention becomes marked.

In the author's series of 5 cases no instance of hemorrhage, peritoneal infection, or other complications has developed because of the use of the Call clamp.

Three figures illustrating the use of the clamp accompany the article.

Nelson M. Percy, Chicago.

SENGSTACKEN, R. F.

Appendicitis in the Small Hospital. S. G. O., Vol. 63, No. 4, Oct., 1936.

The author reports the appendicitis experience since 1920 of a 42 bed hospital in a small community. A total of 602 cases of acute and purulent appendicitis were treated there during that time. The mortality rate was 2.98 per cent for total cases, 0 per cent for chronic, 3.4 per cent for acute and 15 per cent for purulent. Since 1930 it is still lower, viz., 2.1 per cent for total cases, 2.25 per cent for acute and 13.4 per cent for purulent cases. The Battle-Kammerer technique is followed; the stump of the appendix is inverted only in gangrenous cases. Drainage was employed in all pus cases. Ileostomy in the author's opinion should be used only as a secondary procedure but should be done before the small bowel is completely paralyzed. Cecostomy was not used in any case.

In the postoperative management the author feels that patients in small hospitals receive better treatment because they are seen by the surgeon rather than an interne. Sufficient fluid to keep the tongue moist, and repeated transfusions in seriously sick patients, are advised. For



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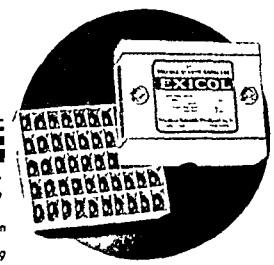
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postoperative distention pituitrin or pitressin are employed. If these fail, a duodenal tube is employed and small amounts of hypertonic saline are instilled into the stomach at 3 hour intervals.

The author concludes that in the treatment of appendicitis the small hospital is superior to its larger brother in the city in that the patients are attended by staff members and graduate nurses rather than internes and student nurses respectively.

Nelson M. Percy, Chicago.

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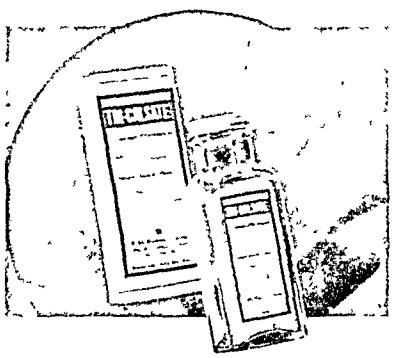
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CLUTE, H. M.

The Problem of Cancer of the Pancreas. J. A. M. A., Vol. 107, pp. 91-97, July 11, 1936.

Recently the surgical removal of small tumors from the pancreas and tubtotal pancreatectomy has been reported. These procedures were carried out because of hyperinsulinism and results have been satisfactory.

Cancer of the pancreas is not a rare disease, constituting 4.8 per cent of the cancer deaths in Massachusetts hospitals in 1928 to 1930. On the whole it constitutes about 3 per cent of all cancer deaths in the United States.

The tumor is most frequently located in the head of the pancreas; some are diffuse, and a few are limited to the tail of the organ. They are generally adenocarcinomas, but scirrhous forms do occur. They metastasize in the usual ways, usually very early. Metastasis is to the regional lymph nodes, liver, lungs and pleura. The tumor as it grows may produce obstruction of the common bile duct and rarely hyperinsulinism and disturbance of intestinal digestion.

The earliest symptoms of cancer of the pancreas is a dull, boring, epigastric pain, digestive distress, epigastric fullness, abdominal distention, and a severe loss of weight in a short period of time. Rarely the first symptom is the onset of jaundice, but usually this, with a palpable tumor in the epigastrium, are signs of advanced conditions.

The diagnosis depends upon the absence of lesions in the gastro-intestinal tract, and the gall bladder as established by X-ray, with the presence of the aforementioned symptoms.

Treatment of the condition is most likely to be successful with surgery, although X-ray and radium have been tried with varying degrees of success. Desjardins and Suave, in 1907 and 1908, advocated a biliary intestinal anastomasis, a resection of the head of the gland and the duodenum, a reuniting of intestinal continuity, and finally the insertion of the pancreas or its duct into the intestine. Whipple, Parsons and Mullins followed this procedure except that they ligated the pancreatic ducts.

Francis D. Murphy, Milwaukee.

EGGERS, C.

Treatment of Carcinoma of the Esophagus. S. G. O., Vol. 63, No. 1, pp. 54-65, July, 1936.

Among the methods of palliative treatment of carcinoma of the esophagus the author mentions general medical care, in which the diet is regulated and balanced carefully; then Gastrostomy when swallowing becomes too difficult and other methods; namely, dilatation, intubation, radiation and electrocoagulation in selected cases with polypoid types of growth.

The radical surgical treatment encounters different problems when the growth is in the cervical, mid-thoracic or lower thoracic regions of the epophagus. Preliminary gastrostomy or jejunostomy is done in all cases.

In cases of carcinoma of the cervical portion of the esophagus with involvement of the hypopharynx and the larynx, complete extirpation of those structures, with their lymph nodes, is the operation of choice. That may be accomplished in a one stage or a two stage operation. In either case the esophagus and trachea open externally. The tracheatomy is permanent but the hypopharynx may be reconstructed later.

In cases of carcinoma of the thoracic portion of the esophagus, devised and first performed by Torck, has been followed with the greatest operative success. It is a transpleural procedure in which the esophagus is divided below the tumor and both ends closed, after which the tumor is delivered through a separate incision in the neck. If the patient survives the operation a rubber tube may be used as an esophagus or a subcutaneous esophagus may be reconstructed on the anterior chest wall.

In cases of carcinoma of the lower esophagus and cardia resection of the tumor mass and esophagus, gastristomy may be done through an abdominal incision or through an abdominothoracic approach as described by Kirchner.

Twenty-three figures and a bibliography accompany the article.

Nelson M. Percy, Chicago.

PACH, G. T., AND SCHARNAGEL, I. M.

The Technique of Gastric Resection for Carcinoma. A critical Review. S. G. O., Vol. 63, No. 2, pp. 189-197, Aug., 1936.

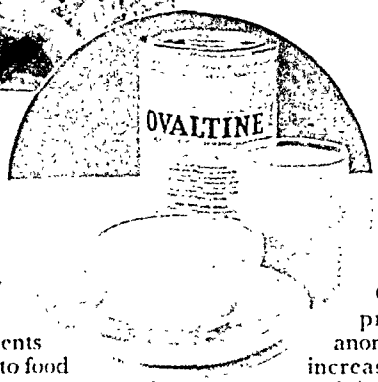
The authors review the history of gastric resection for carcinoma and follow the developments in technic from the original Billroth *I* and Billroth *II* procedures up to those now widely used. The first modifications were made by Schoemaher, Kocher and Haberer-Finney. Each one possessed certain advantages and disadvantages. Later modifications were made by Horsley and Mayo. In the author's opinion the Horsley operation possesses decided advantages over the other operations and in the hands of its master originator is suitable for the majority of carcinomas in the distal third of the stomach.

The Billroth *II* procedure, which made possible the resection of many more tumors of the stomach, has been modified in almost every possible way. The modifications proposed by Polya, Balfour, Moynihan and Finsterer and certain combinations of them are most widely followed today. Very little, in modern literature recommends the Roux, Kronlein or Mikulicz procedures. Sleeve resection of the stomach for carcinoma is rarely used. It is better judgment to excise the portion of the stomach distal to the superior line of excision and make an intestinal anastomosis. Cardiectomy has been performed



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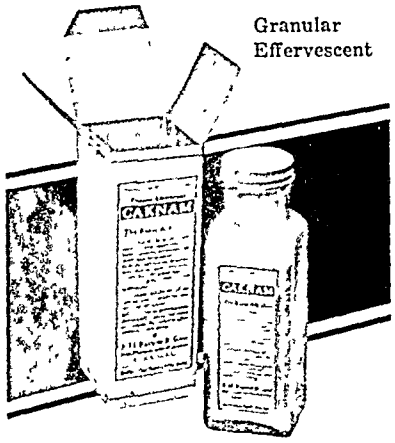
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Total gastrectomy has been performed in a number of instances. The reported mortality of the procedure is 53.8 per cent. Several recent improvements in technique have been made. Moynihan's suggestion that the esophagus be sutured to the jejunum before the stomach is removed has been widely accepted and used. In rare cases it is possible to anastomose the duodenum to the esophagus. When termino-lateral anastomosis between the esophagus and jejunum is effected a complementary enteroanastomosis should always be done between the ascending and descending limbs of the jejunal loop.

A bibliography and five figures accompany the article.

Nelson M. Percy, Chicago.

STEIGMAN, FREDERICK, AND SINGER, HARRY A.

Spontaneous Pneumothorax Simulating Acute Abdominal Affections. Am. Jour. Med. Sci., July, 1936.

The simulation of acute abdominal disease of a surgical nature by common and uncommon thoracic affections with referred pain and by lesions of the spine and spinal nerves is well known. No reference to pneumothorax simulating the "acute abdomen" was found in the American textbooks or systems of surgery, or in treatises dealing with abdominal or thoracic diagnosis, including continental sources, except by Adams, J. E. "Diagnosis and treatment of the acute abdominal disease," 2nd ed., London, Balliere, Tindall, Cox, 1923. In a careful search, only 5 references from the periodical literature since 1911 were found. Among the six instances reported therein, four spontaneous pneumothoraces were erroneously diagnosed primary abdominal disease.

The writers believe that the reported incidence of spontaneous pneumothorax simulating abdominal disease is lower than the actual because of their having seen three such patients in whom they made a correct diagnosis in a relatively short time.

A summary of four previously reported cases and a more detailed account of their own three follows.

Authors comments: Sudden pneumothorax furnishes difficulties in differential diagnosis from the acute abdomen, because the clinical picture of sudden rupture of the lung may be chiefly abdominal. Intense abdominal pain, nausea and vomiting, associated with tenderness and rigidity usually involve a decision as to immediate laparotomy. In four of eight reported cases a history of previous gastro-intestinal disturbance complicated the picture. The thoracic manifestations present in pneumothorax may be associated with acute surgical abdominal affections i.e. sudden pain following violent exertion, reference of pain to the shoulder region, dyspnea, collapse and assumption of the sitting position with the knees drawn upwards.

Error in diagnosis may be avoided by

1. Awareness of the symptom complex in pneumothorax.
2. Careful chest examination in atypical abdominal disease pictures. The detection of a pneumothorax requires expert physical examination.
3. Close attention to the abdominal examination, which may disclose the difference between the hyperesthesia of referred pain and the tenderness of abdominal disease.
4. Suspecting pneumothorax if a history of previous chest disease, especially tuberculosis, is obtained.
5. Routine roentgen examination. This is extremely valuable and quickly done. Unrecognizable and atypical pneumothorax, especially if partial, can best be detected by X-ray and on the film better than fluoroscopically, the latter especially when no pleuritic fluid is present. The exposure should be made at the height of forced expiration, when the pneumothorax becomes most apparent. The roentgen ray serves a double purpose, as it distinguishes a pneumoperitoneum, if present, and thereby aids in the diagnosis of ruptured peptic ulcer, which commonly needs to be ruled out because of its similar history and physical findings.

Marie Ortmayer, Chicago.

SURGERY OF THE LOWER COLON AND RECTUM

MACGUIRE, D. PHILIP.

"Palliative Colostomy." S. G. O., 63:66-68, July, 1936.

A recently reported mortality of 13.4 per cent in 500 cases of palliative colostomy shows that there is still much room for improvement in the handling of such cases. A new operation is described, which has for its outstanding characteristics a tongue shaped flap of skin and fascia extending medially from the center of the usual left inguinal incision, and a method of suturing the lateral peritoneal fold to avoid subsequent herniation and obstruction. An added advantage claimed is that immediate opening of the bowel can be done. Complete details of the preoperative, operative, and post-operative treatment of these cases is to be described in detail in a future publication. Local anesthesia and cyclopropane with the McGill intratracheal catheter are the methods of choice in producing anesthesia in these poor operative risks.

J. Duffy Hancock, Louisville.

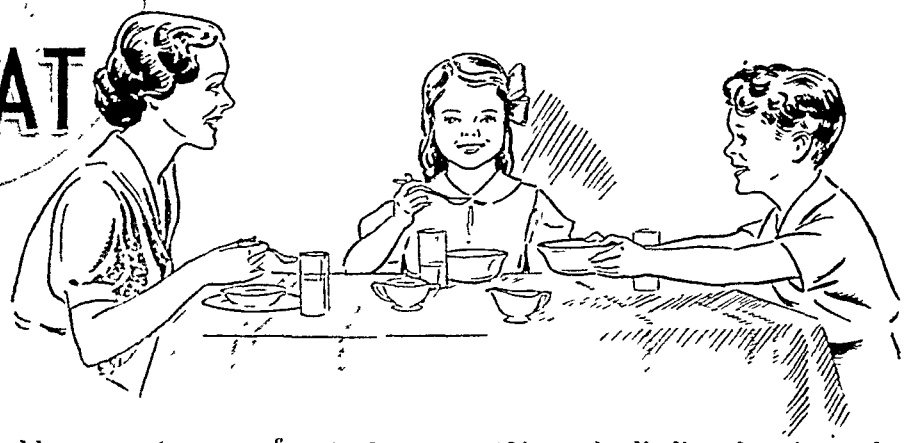
APOLOGY

In the November issue, the address of Dr. Victor C. Meyers was printed at Palo Alto, California, whereas the correct address should have been Cleveland, Ohio.

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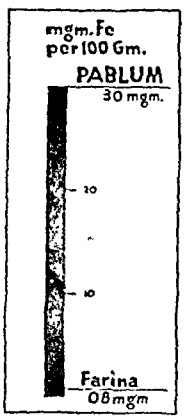


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The Value of Group Psychological Procedures in the Treatment of Peptic Ulcer

By

M. N. CHAPPELL, Ph.D.* J. J. STEFANO, M.D.†
J. S. ROGERSON
and
F. H. PIKE, Ph.D‡
NEW YORK, NEW YORK

FOR many years, the belief has been widespread among physicians that the emotional activity of the patient plays an important part in the maintenance of peptic ulcer, preventing recovery in some cases. Particularly during the current economic depression the attention of the physician has been directed more and more to the psychological elements.

The chief difficulty that has stood in the way of the application of psychological methods to patients with peptic ulcers has been the belief that the psychological problems of these patients are strictly individual and require individual consideration, analysis and training. With the methods most commonly used, months and years are required to return the patient to a state of mental health. As a result of the individual approach, adequate psychological consideration has been effectively restricted to the wealthiest one or two per cent of the population. If each patient constitutes a brand new problem, essentially different in all important respects from every other, the individual approach would seem to be required. Under such circumstances there seems to be little probability that all peptic ulcer patients will ever be in a position to obtain satisfactory psychological attention.

There is some reason for believing, even in the absence of experimental evidence, that there is more commonness than individuality in the important psychological factors in peptic ulcer. There is, on the one hand, the marked commonness of primary and secondary symptoms: the digestive disturbances, the marked feelings of fatigue, the proneness to fear and anger responses and the decreased sexual activity. These are usually present. Constipation and increased susceptibility to pain also appear with notable frequency. On the other hand there is a marked commonness in the important psychological activities. It is usually found: (a) that the patients are worrying and dwelling on their difficulties almost endlessly; (b) that they talk about their disorders on any and all occasions with their friends, relatives and acquaintances, illness being their main topic of conversation; (c) that they are all trying to control one or another aspect of their condition through an "act of will" or "will power."

If these forms of behavior are regarded as the psychological activities which lead to the maintenance of peptic disturbance, one is faced with the problem of discovering the mechanism through which these activities come to influence the gastro-intestinal tract. In view of what is known of the physiological changes in emotion it seems unnecessary to invoke any hypothetical "conversion process." All that is required is to note: (a) that the emotional activity is associated with all of the ideas with which the patient concerns himself; (b) that the emotional activity is subject to modification by learning and (c) that these psychological activities constitute practice or learning mechanisms.

In emotion there appears to be hypermotility, spasm, flaccidity and a decreased blood supply in the gastro-intestinal tract. These might be expected to have some relation to gastro-intestinal health. In peptic ulcer satisfactory recovery necessitates the replacement of injured tissue with scar tissue. But the conversion of the materials of the body into scar tissue is a metabolic function. The body, or a part of it, cures itself when the conditions are favorable. The conditions favorable for recovery are rest of the diseased parts and an adequate blood supply. It is readily apparent that bodily rest and emotional hyperactivity are incompatible. The body cannot rest when the brain is in a state of agitation, for the brain cannot be active continuously in unpleasant emotional states without tending to stimulate efferent pathways. It would seem then, that if the emotional hyperactivity could be reduced, the conditions would result which would enable the body to cure itself more readily.

I. THE EXPERIMENTAL TECHNIQUE

In this experiment 52 patients were employed. All had the characteristic subjective signs and abnormal physiology as well as some of the objective signs of peptic ulcer. Those subjects who were examined and found to have no objective signs but only the abnormal physiology and subjective signs will be considered in another paper. This one will restrict itself to the 52 patients who appeared to be organic cases. All had

Respectively of *Columbia University, †Brooklyn Hospital and ‡Columbia University.
Submitted August 14, 1936.

been subject to peptic disturbance for a protracted period of time and had shown themselves to be resistant to satisfactory treatment through medication and diet alone. All had been diagnosed as peptic ulcer at least once before the diganosis was confirmed in the present experiment. All cases were ambulatory. No patient was accepted in whom the ulcerous condition was deemed to require surgical treatment. The attitude towards surgical treatment was that it was to be employed only if there was little probability of successful treatment with medication and the procedures outlined below. The attempt was made to recruit the patients from that seventy or so per cent of the peptic ulcer cases who "do not recover."

Diagnosis of peptic ulcer was made by means of the following procedures: 1. Complete medical history and physical examination; 2. Test meal for the determination of hydrochloric acid, total acid, mucus and food retention; 3. Stool examination where it was deemed advisable; 4. Fluoroscopy following a barium meal and 5. X-ray plates in doubtful cases.

The corroboration of the diagnosis of ulcer was made if the subject gave a typical ulcer history, showed hyperacidity and a niche or protrusion area in the stomach, in the case of stomach ulcer; or, in the case of duodenal ulcer, constant deformity of the cap in spite of relaxation with atropine to a point of disaccommodation, or a protrusion area or niche in the post pyloric region, or blood in the stomach or stool. All subjects were treated medically as private patients, but without change.

Following the diagnosis, all of the patients were put on a standard dietary and medical *regime*. The medication consisted of gastric mucin. Its supposed function was to neutralize hyperacidity and form a mucus coating on the mucous membrane wall and so plug up some of the gland ducts. The essential features of the diet were frequent feedings of moderate amounts of foods consisting of the high caloried lacto-farinaceous type and pureéd vegetables. In some cases some form of alkali was given in conjunction with the gastric mucin.

The subjects were then divided into two groups, an experimental group of thirty-two and a control group of twenty. The patients in the experimental group were then trained daily, seven days a week for a period of six weeks while nothing of a psychological nature was done for the control group. All differences between the experimental and control groups were in favor of the control group as may be seen from the following comparison:

	Experimental	*Control*
1. Age		
Range	26 - 63 years	27 - 59 years
Average	44 years	42 years
2. Period of some peptic disorder		
Range	2 - 30 years	2 - 25 years
Average	12 years	8 years
3. Period of recognized peptic ulcer		
Range	2 - 21 years	1 - 25 years
Average	8 years	7 years
4. Previous surgical treatment for peptic ulcer		
Number of cases	5	0
5. Number of previous reliable diagnoses of peptic ulcer		
Range	1 - 6 years	1 - 4 years
Average	2.6 years	1.6 years

II. THE TRAINING PROCEDURES

The experimental group was divided into two classes, each of which was in charge of one instructor. Since there were minor variations in the methods of the two instructors only a statement of the common features employed by the two will be given here. The primary difference was in the mode of explanation.

Six measures were employed in the attempt to induce the conditions desired in the patients. It is apparent that at least three corrective measures are necessary. A procedure for the control of each of the activities, worry, discussion and the use of "will power" are essential. Three others which give evidence of benefits were also employed.

1. *Control of worry:* While there are many and diverse ways through which worry may be eliminated, the procedures employed here are simple and direct. It is necessary that the patient learn to substitute some less unpleasant form of activity for the worry *behaviour. Such a substitution appears to be learned* with facility by most people in about three weeks, when they are properly directed and sufficiently well motivated; which is to say, when their illness makes them sufficiently uncomfortable.

The patients were instructed to pick out some period of their lives about which they had many pleasant, or not unpleasant, recollections. Each time they found themselves worrying, which was many times a day in the early stages, they were to direct their thoughts to the period of their lives that they had chosen and concern themselves as far as possible with the events of that period. For most people the recollection of childhood experiences serves well for this purpose. Any other period might be used equally well. Each time they found themselves worrying they were instructed to turn their attention to the recollections they had chosen and continue along that line until the thoughts were again back on their bothersome situations, when the attention was again to be turned to the chosen period. The patients had no great facility in diverting their thoughts for the first few days, but after three or four days they found it became easier. As with everything that is learned, facility in diverting the thoughts comes only with practice.

2. *Control of Discussion:* Despite the extent to which the patients discussed their difficulties with others, the control of discussion did not prove difficult. Once the patient learned that discussion of his difficulties was not in the interest of his eventual recovery he took immediate steps to eliminate it. To attain this end it was recommended that he seek the cooperation of the family as well as that of his close friends, who proved to be so weary of listening to his tales of woe that they were pleased to obtain the relief. Occasionally, wives and mothers required some persuasion. Before many days, any tendency on their part to remind the patient of his condition was met with anger on the part of the patient. This proved to be sufficiently persuasive to control even the most stubborn wife or mother.

3. *Control of Effort:* To eliminate effort it was necessary to show the subjects what they were doing to themselves through attempts to use their imaginary "will-power." The training here dealt with the specific situations in which they might be attempting to gain their ends through effort or a display of "mastery." For example, in attempting to divert attention from his worries the patient will commonly try to force his

thoughts along the new channels. The futility of this was demonstrated. He was then shown how to procede with a minimum of effort, since effort is in opposition to visceral rest. They were instructed not to make martyrs of themselves or fail to relieve emotional tensions because they felt that to do it was to "baby" themselves. They were to "baby" themselves on any occasion when they desired to do so. Many specific situations required consideration. The following is an example: One might have developed the habit of placing a glass of milk on the night table when he went to bed so he would have it handy when, and if, he should awaken with a pain in the epigastrium during the night. He may have felt that this was a bad habit and that he should take steps to break himself of it. While he would like to have the milk there, he felt that he was losing his "will" in these matters and he should assert himself against himself. This tendency to "assert himself" was an attempt to relieve the situation by effort. If he had the slightest inclination to take the milk to bed, he was instructed to do so whether he really needed it or not. He was more apt not to need it if it was there. The "habit" was insignificant, its development was unimportant. The important thing was that he should not go to bed with apprehensions of pain and absence of the remedial milk. In such cases, the patient was to be guided by his emotions, not by his ideas or those of some one else. Similarly with food when the diet was to be expanded. If there was some food of which he was afraid, he was to avoid it until he was largely rid of his fear, even though the physician may have told him that it was right for him to eat. When the time came that he wanted to try it, he was to take only a little of it, for only a little would give rise to only a little apprehension and the chances of success were relatively large. Once it had been successfully eaten he would be confident of the ability of his stomach to handle it and the apprehension would disappear largely or entirely.

Some procedures such as the above would be essential to satisfactory control of the emotional activity, but they do not exhaust the possibilities. Three others were employed.

4. *Explanation or Insight:* We tend to be most emotional about those adverse situations which we do not understand. Daily lectures for periods of forty-five minutes were devoted to the education of the patients with regard to the nature of thought and its influence on bodily activity, the patient's manner of reacting to the common situations in his life, the origin of his ideas and emotional reactions and many other factors bearing on the situation in hand. The value and efficacy of the medication and diet were frequently extolled. The procedures used were explained in detail and the manner of their operation illustrated whenever possible. Through these lectures the patient came to understand himself and the part he could play in maintaining his own health.

5. *Self-assurance or Self-suggestion:* Since each patient had built up an idea of himself as a very sick person whose eventual recovery was doubtful, it seemed desirable to have him build up a different conception of himself. The constant assurance to himself that he is recovering, by talking aloud to himself, offered an important possibility. For this purpose a phrase similar to that recommended by Coué was suggested for repetition while the patient was in bed in the evening and morning. While it would be difficult to say with certainty exactly what the mechanism is through which self-assurance achieves its effect there is one important factor that has sometimes been overlooked. Since emotional hyperactivity is only one aspect of a condition of which loss of confidence is another, everything must be done that can be done to build up the confidence of the patient, especially in himself. The self assurance and learning to divert his attention were things that the patient was doing for himself, through which he aided his own recovery. These things that the patient did for himself appeared to restore his confidence in himself to a marked degree and eventually to leave him independent of those who instructed him. In the light of the dependence frequently found in patients after education by some other psychological methods this may be significant.

6. *Assurance or induced suggestion:* The patients were given daily assurance of their ability to gain the ends they desired. This assurance covered digestion, absorption, sleep, vigor, elimination of emotional ideas and pains, correction of constipation and the development of confidence. This procedure goes back at least to Bernheim and is commonly called "induced suggestion." It appears to have marked value in producing feelings of well-being in the patient. No attempt was made to induce sleep in the patients while assuring them.

III. RESULTS

The patients in the experimental group were given thoroughly to understand that they were undertaking an experiment and that while there seemed good reason for believing that they might be benefited by the training, that this was the point which they were to determine. The attitude of the patient was that it was an experiment; that it was one more thing to try. None of them believed that it would do very much for him but since he had tried everything else without much gain he would follow instructions closely and give this a good try. About fifteen subjects dropped out of the experimental group because they did not believe there was a chance of their efforts repaying the expenditure of time, even though the lectures were given in the evening so as not to interfere with the working activities of the patients, and both the psychological training and the medical attention were gratis. These patients dropped out usually after the first or second lecture. The thirty-two who went through the six weeks gave the heartiest cooperation, regardless of what they themselves believed of one or another of our recommendations.

A. Immediate Results: After being trained for three weeks, at which time all of the subjects of the experimental group, with one exception, were free from subjective symptoms, the expansion of the diet was recommended. This was done in a given order for a week and then the patient directed his own expansion for the next two weeks. At the end of the six weeks' training period all but two of the thirty-two patients were eating about anything they wanted. Of these two, one expressed a preference for a slower expansion and required about two months to get back to a normal diet. The other showed no appreciable improvement throughout the experimental period nor subsequently. Both his peptic condition and his environmental situation were very severe. He was an elderly Italian, with a mild hemorrhage and who was

unemployed and about to lose his home on foreclosure and whose wife was about to have a baby.

The control group of twenty subjects remained on medication and diet for four weeks before the expansion of their diet was recommended. At this time all of the members of the control group were free from subjective symptoms. Within two weeks of the time that the expansion was started all but two had recurrence of symptoms. Of these two, one would not follow the recommendations for the dietary expansion, believing that it would certainly make him ill again.

A comparison of these results enables one unhesitatingly to draw the conclusion that the group procedures have a marked value in enabling peptic ulcer patients to rid themselves of their subjective symptoms and return to a satisfactory diet and mode of living.

B. Remote Results: It is frequently stated that peptic ulcers are never "cured." The fact that the patient may have a recurrence of his disorder is offered as evidence of this. On the basis of recurrence one might also say that pneumonia or a broken leg are never "cured." Under the proper conditions the patient may induce the same disorder again. If by "cure" one means that the patient in some way is put in such shape that he can never again have the condition, then one may certainly say that peptic ulcer is never cured. The fact that he has been able to develop the condition once is fair evidence that under the proper conditions the peptic ulcer patient can do it again.

A further question as to the value of the psychological training arises on this basis. Does the training aid the patients in maintaining in themselves those conditions which are in line with their continued health, and to what extent? To answer this question it is necessary only to permit a lapse of time. The interval of time between the end of the training period and the second examination varied from six to ten months, with an average of eight months. At the end of this interval complete tests for objective signs were again made.

Of the 31 patients in the experimental group who were well at the end of the training period, one had a recurrence at the end of three months which was as severe as his original condition. Four others were not examined. Three of these four reported that they were in excellent health but were unable to come for re-examination at the time requested. The fourth could not be located.

The remaining 26 were found to be in excellent health. Twelve of these reported one or more short periods of a return of the symptoms. The symptoms were reported to be mild and easily gotten rid of through return for a few days to the medical and psychological procedures recommended. The average duration of these recurrences was three days. The recurrences followed immediately after such events as an explosion of gas in the home, illness of a wife, death of a mother, breaking a finger, amputation of a toe, loss of a job, bankruptcy, and others of a simliar nature. All of these subjects, with the exception of the one whose recurrence was severe, reported themselves to be completely confident of their ability to take care of themselves if any symptoms did arise.

Since only two subjects in the control group survived the first part, our control group for this part of the expermient was not impressive. Both of these two control subjects had recurrences as severe as their original conditions within two months following the former seven weeks period.

Eight months is hardly sufficient time to follow peptic ulcer patients to determine how well they keep themselves. A final checkup was made at the end of three years. It is not planned to follow these subjects further. The following results were obtained at the end of the three year period.

Three of the experimental patients could not be located.

Ten have remained symptom free for the whole period. "Symptom free" is defined in this experiment as the state in which the patient has not had a return of symptoms for a day. Five others remained nearly symptom free. The average number of recurrences in these five were 1.8 per year. The average length of the recurrences were 4.9 days. The symptoms in all cases were reported to be mild and easily controlled. Each of these five considered himself to be in excellent health. The amount of disorder observed in these five is probably little, if any, more than will be found in the average of the population at large, which is to say that they are about normal.

Nine patients reported numerous recurrences of mild symptoms. Two reported single recurrence of hemorrhage from which they recovered quickly. The average length of recurrence for these eleven subjects was about six days. All but two considered themselves to be healthy and completely confident of their ability to handle successfully the symptoms which might arise, through recourse to the diet, medication and psychological measures.

Two others (including the one reported at the end of the eight month check-up) have had recurrences as severe as the original condition, from which they have not satisfactorily recovered.

From these remote results it is possible to conclude that not only is the group psychological training of value in amelioration of the symptoms in the first instance, but that it aids the patient in maintaining himself in a healthy condition for at least three years after the training. It seems possible to conclude, also, that the belief that emotional activity plays an important part in the maintenance of peptic ulcer is justified.

IV. REMARKS

From these results may be drawn a number of inferences which are important to psychology as well as to physiology. These will be considered in another publication. On the medical side there are some further observations that are worthy of note.

In cases of pyloric obstruction caused by scar tissue, a progressive obstruction is commonly observed. Several of the patients showed this type of obstruction with concommittant spastic phenomena. These have not, apparently, become any worse. Two cases were notable in this connection who had previously shown a marked retention at the end of six hours. After three years they showed some obstruction but the residual barium at six hours was slight. All of the cases who presented the symptoms of pyloric obstruction had vomiting before the experiment. In none of these had there been vomiting during the three years.

In about 20% of the cases the duodenal cap remained deformed although the patients were at the time free of subjective symptoms and in some cases

had been symptom free throughout the three years. The impression obtained from this is that the persistent deformity is caused by scarring in the first portion of the duodenum.

Perhaps the most significant medical finding is that in about 40% of the cases, at the end of the three year period what has commonly been considered as organic pathology could be observed without any subjective symptoms. This would seem to support the view that a diagnosis of ulcer should be made on the basis of how the patient feels as well as on his appearance before the fluoroscope.

The absence of subjective symptoms does not, however, exclude serious organic pathology. An elderly bookbinder, unable to work, volunteered for the experiment and was found to be in an advanced stage of carcinoma. His subjective symptoms were severe. Regularly each night he arose from bed five times for food to relieve his pains. Because of his circumstances it was deemed unwise to reveal to him his true condition. Rather, he was referred to the group with the expectation that he would attend until he lost interest and dropped out. To our great surprise he was free from his subjective symptoms at the end of seven weeks, was eating whatever he desired and returned to work at his trade. He remained free from his pains and died of carcinoma two months later. This case throws considerable light on the supposed cures of carcinoma through the agencies of magic, religion and other forms of psychotherapy.

Serum Lipase: Its Diagnostic Value

By

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ABOUT a year ago Osterberg and I (1) made a preliminary report on the value of determinations of serum lipase in the detection of pancreatic disease. We found that an increased activity of lipase in the serum was good evidence of disturbed pancreatic function, especially when such an increase was associated with signs and symptoms of cholecystitis, choledocholithiasis, cholangeitis, and pancreatitis. At this time I want to present additional data on the activity of lipase in the serum of normal persons and of patients with various diseases. While the report by no means answers all the questions that might be asked concerning the clinical application of the procedure, additional experience permits its presentation again as a satisfactory aid in the detection of pancreatic dysfunction.

METHOD

The degree of lipase activity of the serum was determined by the amount of olive oil hydrolyzed by a given quantity of serum in a given period of time. A modification of the Loevenhart method used by Cherry and Crandall (2), with a slightly different buffer solution, has been described previously.

VALUES FOR LIPASE IN THE SERUMS OF PATIENTS WITHOUT KNOWN ABDOMINAL DISEASE

The serums of two groups of persons without demonstrable organic abdominal disease have been examined for lipase activity. Group 1 contained 111 persons who did not have abdominal symptoms; group 2 contained seventy-two persons who had abdominal symptoms of a functional nature. The range is between 0.2 c.c. and 1.5 c.c. twentieth normal sodium hydroxide per 1 c.c. of serum. The most frequent values are 0.6, 0.7, 0.8, and 0.9 c.c. Comparatively few values were obtained that were less than 0.4 c.c. or more than 1.2 c.c.

The findings indicate that an olive oil splitting lipase is normally present in the serum of man. Such a finding is contrary to the experience of Crandall and Cherry (3) or of Jergesen and Simonds (4). Cherry and Crandall found that the serums of forty of forty-six patients did not reveal any trace of olive oil splitting lipase, and that the remaining six gave values of 0.3 c.c. or more. Jergesen and Simonds found that twenty-two of twenty-five persons had values for lipase of less than 0.3 c.c. In other words, these investigators found that the serum of man rarely contained an olive oil splitting lipase as is the case in dogs.

VALUES FOR SERUM LIPASE IN THE PRESENCE OF PANCREATITIS

With the development of acute pancreatitis, the values for serum lipase rise above the normal range and have reached 10.2 c.c. per 1 c.c. of serum. The curves in Figure 1 illustrate the behavior of values for serum lipase in cases of pancreatitis with and without disease of the biliary tract. It will be noticed that the rise is prompt, the values being high even on the day of the attack (Curves 1, 3, and 4), and that a fall in the value of lipase occurs within two or three days. The fall may be precipitous (Curves 1, 2, 3, and 4), and in some instances it may be followed by a secondary rise (Curves 1 and 4). In such cases, the clinical symptoms, including pain, fever, and leukocytosis, warrant the belief that the process remains active. In most cases normal values are obtained in the third week. In three cases slightly elevated values have been found later than three weeks after the attack, but again in these cases there is clinical evidence to indicate that the process has not been steadily resolving since the onset of the attack. In short, values for serum lipase following an attack of pancreatitis rise rapidly and they then fall rapidly or slowly to normal levels, which are usually reached within three weeks following the attack unless the pancreatitis

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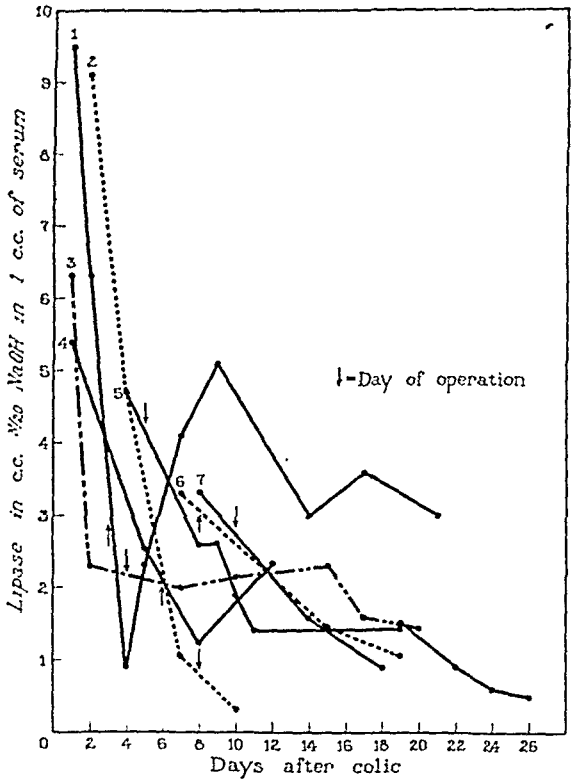


Fig. 1. Curves showing behavior of values for lipase in the serums of patients with acute pancreatitis.

fails to resolve. In a general way the more recent an attack, the higher the values for lipase.

Any explanation of the increase in the values for serum lipase must be theoretical. It may be presumed, however, that this increase is due either to absorption of secreted juice as a result of blockage of the ducts or to absorption of the enzyme from disintegrating pancreatic tissue. Crandall and Cherry (5) have suggested that pancreatic injury liberates a co-enzyme which activates normal blood lipase.

Studies on serum lipase had been carried out before operation in forty-five cases in which the surgeon reported pancreatic disease at operation. In the first twenty cases the clinical or pathologic data pointed to an acute process and the values were increased. In seventeen of the twenty cases in which the values were elevated the readings were obtained within ten days of the onset of the acute attack of upper abdominal disease or during a period of persisting symptoms. In the twenty-first case there was unimpeachable evidence of recent acute pancreatitis, yet the lipase values were normal. In this case, the process was acute and fulminating, and the patient died after ten days. At necropsy, the pancreas was completely necrotic. The rapid and complete disintegration of the pancreas, with destruction of lipase-producing tissue, may be advanced in explanation of the failure of the values for serum lipase to increase. In the remaining twenty-four cases the changes in the pancreas observed by the surgeon were slight and chronic or the determination of serum lipase was carried out fourteen to sixty days after the attack, a period of time sufficient for the lipase value to return to normal in spite of the apparent acuteness or subacuteness of the process in the pancreas. In these twenty-four cases the values were normal.

It is clear that elevated values are associated with acute and subacute pancreatitis, that such rises may fail to take place if pancreatic necrosis is extensive, that the values return to normal usually somewhere in the third week if not earlier, and finally that chronic pancreatitis does not cause elevation of values. So far I have been unable to find any evidence suggesting that in chronic pancreatitis the values for serum lipase are decreased below normal. In the few cases of extensive atrophy and calcification of the pancreas in which I have had the opportunity to determine the values for serum lipase, they have been within the normal range. The test appears to be quite accurate in the diagnosis of acute pancreatitis with or without associated disease of the gall bladder. In only one case out of twenty-one in which there has been clinical and pathologic evidence of the acuteness of the pancreatic process has elevation in the values for serum lipase failed to take place whenever the determination was made in the active phase of the disease.

VALUES FOR SERUM LIPASE IN MALIGNANT DISEASE OF THE PANCREAS

Increased lipase values have also been found in the serum in fifteen of forty-one cases in which malignant disease of the pancreas was present, the increases ranging as high as 6.4 c.c.

The behavior of serum lipase in cases of carcinoma of the pancreas involving the head of the gland and producing painless jaundice are graphically shown in Curves 3, 4, and 5, Fig. 2. In such cases the values for serum lipase tend to remain elevated, sometimes forming almost a flat curve, which persists after the relief of obstruction of the common duct by cholecystgastrostomy and suggests that obstruction of the pancreatic duct accounts for the elevation. In an occasional case (Curve 2, Fig. 2), in which the clinical picture undoubtedly justified a diagnosis of obstructive jaundice resulting from stone in the common duct and cholangeitis with pancreatitis, and in which the surgeon found a mass at the head of the pancreas so typical grossly of carcinoma that cholecystgastrostomy was performed, the rapid decline in the value for serum lipase resembles closely the behavior of serum lipase in the presence of acute pancreatitis. It is possible that superimposed pancreatitis may have markedly altered the behavior of serum lipase often seen in cases of carcinoma of the head of the pancreas. Further observations, together with the findings at necropsy, are needed to clear up this point.

Increased values for serum lipase also have been found in three of five cases of carcinoma of the ampulla of Vater. The behavior of serum lipase in these few cases is illustrated in Curves 1 and 6, Fig. 2. Curve 1 was constructed with the values obtained for serum lipase in a case in which the history of recurrent attacks of pain, with chills, fever, and jaundice, warranted a clinical diagnosis of cholecystitis with stones, obstructive jaundice attributable to stone in the common duct and cholangeitis. The surgical finding of apparent malignancy of the head of the pancreas was a complete surprise. Necropsy confirmed the presence of cholecystic disease and disclosed the malignant growth in the ampulla of Vater. Curve 1 differs

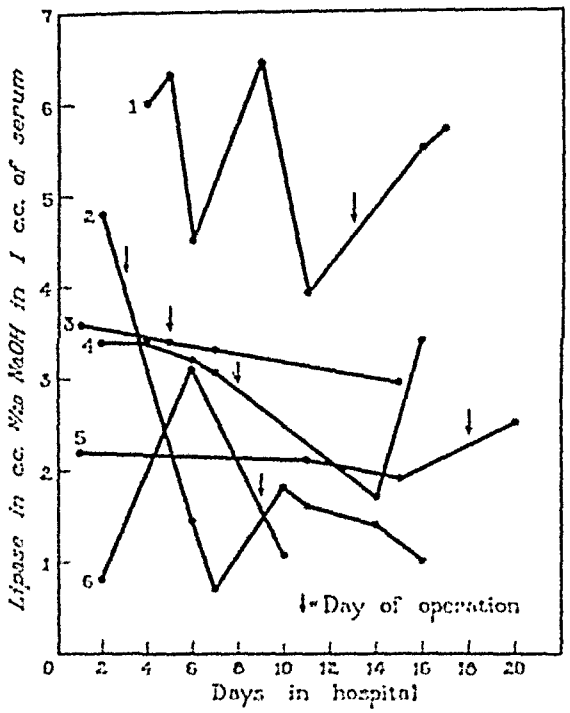


Fig. 2. Curves showing behavior of values for lipase in the serums of patients with carcinoma of the head of the pancreas or carcinoma of the ampulla of Vater.

from the curves seen in cases of carcinoma of the head of the pancreas by its irregular fluctuations, and from that seen in cases of pancreatitis by remaining at approximately the same average elevation for twenty-one days. The same rapid fluctuations in the values for serum lipase are seen in Curve 6, Fig. 2. The fluctuations are apparently related either to recurrent exacerbations of associated pancreatitis or to intermittent opening and closing of the ampulla of Vater.

VALUES FOR SERUM LIPASE IN DISEASES OF THE BILIARY TRACT

In Table I are listed 135 cases of disease of the biliary tract in which pancreatitis was not discovered at operation. In 116 of the 135 cases the values for serum lipase were normal; in the remainder they were elevated. Normal values occurred in all the various types of disease of the biliary tract. For this reason, some explanation other than disease of the biliary tract must be sought to explain the increased values in the nineteen cases. Crandall and Cherry have shown that an enzyme capable of splitting olive oil is present in appreciable amounts only in the tissues of the pancreas, liver, intestinal mucosa, and spleen. Disease of the spleen and of the intestinal mucosa does not occur in these cases. In view of Crandall and Cherry's work, the explanation must, therefore, be found in disease of the pancreas or liver.

It was not known that pancreatic disease was absent in any of the nineteen cases, for the condition of the pancreas was not described by the surgeon. In each of the nineteen cases the common duct was diseased. In seventeen of the nineteen cases the elevated values were obtained in the course of acute attacks of upper abdominal pain accompanied by symptoms and signs of inflammation, or within ten days of the onset of the attack, or in the course of exacerbations of jaundice accompanied by chills and fever. If the pathologic changes in the pancreas in these cases were known I believe the elevated values would be associated with pancreatitis or obstruction of the pancreatic duct by stone in the common duct.

Disease of the liver is a possible explanation in two of the five cases of stricture of the common duct. In these two cases there was extensive hepatic injury; however, as will be seen later, elevation of the value for serum lipase in hepatic disease is comparatively infrequent, and when present, theoretically at least, may be attributable to associated pancreatitis. Under the circumstances it seems that, associated with symptoms of disease of the biliary tract, elevated values for serum lipase in all probability indicate pancreatic dysfunction and, in the great majority of cases, dysfunction attributable especially to inflammation of the pancreas.

VALUES FOR SERUM LIPASE IN DUODENAL ULCER

Elevated or increased values for serum lipase occurred in five, or 7 per cent, of the seventy-one cases of duodenal ulcer (Table I). The occurrence of elevated values for serum lipase in the five cases of duodenal ulcer is not surprising considering the close proximity of the duodenum to the pancreas. This increase, however, seems to be much less than that found by Jergesen and Simonds, using 0.2 c.c. twentieth normal sodium hydroxide as the upper limit of normal. They found that thirty-eight (76 per cent) of fifty cases had increased values for lipase in the serum.

The involvement of the pancreas by the process in the duodenum seems to be the explanation for the increased values, at least it was so in three of the five cases in which the values were elevated. In these three cases the surgeon found that a subacute duodenal ulcer had perforated to the pancreas and formed a mass in the first case; that an acute duodenal ulcer had perforated to the gall bladder, producing acute cholecystitis, and to the pancreas, forming a mass of considerable size, in the second case; and that an acute duodenal ulcer, associated with acute purulent cholangeitis, was present in the third case. Of the two remaining cases, in one, operation was not performed, and in the other the surgeon merely described the chronic duodenal ulcer and did not mention the pancreas.

VALUES FOR SERUM LIPASE IN HEPATIC DISEASE

Elevated values occurred in five, or 13 per cent, of thirty-seven cases of hepatic disease (Table I). The diagnoses in these five cases were: hepatitis with jaundice due to Malta fever, hepatitis with jaundice due to lobar pneumonia, toxic hepatitis due to cinchophen poisoning, toxic cirrhosis of unknown etiology, and biliary cirrhosis. Elevation of the value for serum lipase in hepatic disease seems to be the exception rather than the rule, contrary to the experience of Cherry and Crandall.

Crandall and Cherry suggested that the lipase may be absorbed from the injured liver or that the injured liver fails to remove the lipase, which naturally passes into the blood from the gastro-intestinal tract whereas the normal liver acts as a barrier to this substance.

Consideration must be given to other explanations for the increased values in hepatic disease, for many other cases of hepatic disease, with much more destruction of hepatic parenchyma than was found in these five cases, were not associated with increased values for serum lipase. In the cases of Malta fever and lobar pneumonia, it seemed just as logical to explain the elevated values for serum lipase on the basis of a secondary pancreatitis as it was to explain the jaundice on the basis of an associated hepatitis. It is even possible that the toxic or infectious agent producing the hepatitis in the remaining three cases likewise produced a disturbance of pancreatic function. Whichever explanation for the increased values in hepatic disease is correct, certainly from a clinical standpoint these occasional elevations are not very important. In the case of Malta fever and pneumonia, the elevations were not of diagnostic interest. In the other three cases, the elevations were so slight and inconstant that one's clinical judgment could hardly have been influenced by the findings.

TABLE I

Values for serum lipase of patients with disease of biliary tract, duodenal ulcer and hepatic and various other diseases

	Cases in which lipase was more or less than 1.5 c.c. of N/20 NaOH per 1 c.c. of serum		
	Less than 1.5 c.c.	More than 1.5 c.c.	Total Cases
Disease of biliary tract without discovery of pancreatitis on operation:			
Chronic cholecystitis with or without stones (operation not performed)	12	0	12
Chronic cholecystitis without stones	14	0	14
Chronic cholecystitis with stones	17	0	17
Chronic cholecystitis with or without stones, stone in common duct or cholangeitis	13	2	15
Stone in common duct or cholangeitis	18	5	21
Acute cholecystitis with or without stone	11	0	11
Acute cholecystitis with stone, stone in common duct or cholangeitis	3	5	8
Stricture of common duct	16	5	21
Carcinoma of gall bladder or ducts	14	2	16
Total	116	19	135
Duodenal ulcer:			
Operation not performed	35	1	36
Operated	31	4	35
Total	66	5	71
Hepatic disease:			
Cirrhosis	19	1	20
Hepatitis	13	4	17
Total	32	5	37
Malignant disease:			
Stomach	24	1	25
Large intestine	9	0	9
Abdominal carcinomatosis	7	0	7
Breast	5	0	5
Urinary bladder	2	0	2
Uterine cervix	1	0	1
Total	48	1	49
Miscellaneous diseases	82	3	85

VALUES FOR SERUM LIPASE IN MALIGNANT DISEASES

Normal values for serum lipase were obtained in forty-eight cases of carcinoma of the stomach and large intestine, abdominal carcinomatosis, and carcinoma of the breast, urinary tract, and uterine cervix (Table I). In one case of carcinoma of the stomach there was a slight elevation of the value for serum lipase. In this case, carcinoma of the stomach had perforated to the pancreas. The involvement of the pancreas probably explains this exception to the general rule that malignant processes other than in the pancreas itself are not associated with elevations of the serum lipase.

VALUES FOR SERUM LIPASE IN VARIOUS OTHER DISEASES

Under the heading "miscellaneous diseases" in Table I are grouped eighty-five cases. Included were patients with indeterminate gastric complaints, questionable cholecystitis, and syndromes following cholecystectomy; patients who had previously undergone cholecystectomy, with or without pancreatitis at the time of operation; patients who were pregnant; and patients with healed duodenal ulcer, gastric ulcer, hypertrophic gastritis, gastrojejunal ulcer, primary duodenal obstruction, congenital cystic liver, residual hepatic dysfunction, sprue, diabetes mellitus, hyperinsulinism, partial intestinal obstruction, acute appendicitis, acute intestinal obstruction, Addison's disease, Hodgkin's disease, abdominal abscess, pulmonary abscess, puerperal septicemia, peritonitis of undetermined etiology, hyperthyroidism, myxedema, and pernicious anemia. In eighty-two of these cases the values for serum lipase were normal. In only the remaining three cases were the values elevated. The first was a case of peritonitis of indeterminate etiology, the second a case of puerperal septicemia, and the third a case of pulmonary abscess. In these three cases, in this stage of the study of lipase, the elevated values for serum lipase are probably best explained on the basis of pancreatitis secondary to an infectious process.

Crandall and Cherry reported that in twelve of nineteen cases of multiple sclerosis, the values for serum lipase were increased above the limit accepted by them as normal. This series does not contain cases of that disease.

SUMMARY AND CONCLUSIONS

A simple titration method for the determination of values for serum lipase, using olive oil as a substrate, has been applied clinically to normal persons and to patients with a wide variety of diseases.

The upper limit of the values for lipase in the serums of persons without pancreatic disease appears to be about 1.5 c.c. of twentieth normal sodium hydroxide.

Elevated values for serum lipase have been found in 95 per cent of the cases of acute pancreatitis, in 36.5 per cent of those of carcinoma of the pancreas, and in 60 per cent of those of carcinoma of the ampulla of

Vater. An increased activity of the serum lipase appears to be a very efficient test for pancreatitis, less so for malignant disease of the pancreas. The increased values in these diseases followed inflammation of the gland or obstruction of the pancreatic duct by carcinoma. Elevated values appear in cases of acute inflammation of the pancreas immediately after the onset of the attack, and as a rule they decline to normal levels within three weeks or even earlier in the course of the disease. It would appear that elevated values occur in acute inflammations of the pancreas so long as an adequate amount of lipase-producing tissue is present, and less frequently in malignant disease, depending on the presence or absence of obstruction of the pancreatic ducts or on the presence of inflammation associated with a malignant process in the pancreas.

An elevated value for serum lipase does not of itself distinguish between inflammation and malignancy of the pancreas. The interpretation of the increase in lipase activity of the serum must depend on the associated clinical findings. If the symptoms point to inflammation of the biliary tract, the elevated values for serum lipase will usually indicate an associated pancreatitis or obstruction of the pancreatic duct by a stone impacted in the ampulla. If the symptoms point more to inflammation of the pancreas than to inflammation of the biliary tract, elevated values for serum lipase should be confirmatory evidence of the clinical suspicion of pancreatitis. In the presence of a painless jaundice, elevated values for serum lipase will usually point to the presence of carcinoma of the head of the pancreas.

The behavior of the values for serum lipase seems to be somewhat distinctive of the type of pathologic condition present. If these values rise rapidly following an acute attack of upper abdominal pain, and then fall gradually or rapidly to normal levels, such behavior favors the presence of pancreatitis. If the values for serum lipase in the presence of a painless jaundice are increased and sustained at a fairly constant level, carcinoma of the head of the pancreas is probably present. If the values for serum lipase are elevated but fluctuating, carcinoma of the ampulla of Vater must be suspected. An acute pancreatitis associated with malignant disease of the pancreas may alter the type of curve and obscure the diagnosis.

Values for serum lipase were elevated in 7 per cent of the cases of duodenal ulcer. Such elevations in this disease probably point to an acute perforation of the ulcer to the head of the pancreas, or point to an associated inflammation of the common duct with pancreatitis.

Disease of the liver was associated with elevated values for serum lipase in 13 per cent of the cases. The elevation is apparently due either to destruction of the hepatic parenchyma or to the presence of an associated pancreatitis. Clinically, up to the present time, these elevations have not proved confusing, and as a rule they have been so slight and inconstant that clinical judgment was not influenced.

The determination of serum lipase activity promises to be a very valuable procedure in the laboratory diagnosis of acute pancreatitis and of pancreatic malignancy, especially when correlated with the clinical symptoms. So far it has proved of greater value in the diagnosis of acute or subacute inflammation of the pancreas than any other procedure we have used.

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SECTION II—*Experimental Physiology*

Prophylactic Treatment of Peptic Ulcers Produced Experimentally by Cinchophen*

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PREVIOUS studies by Van Wagoner and Churchill and by us have shown that the administration of cinchophen is an effective method for the production of chronic peptic ulcers in dogs. In a series reported by us peptic ulcer developed in approximately 96 per cent of the animals following oral administration of the drug (3). A few of the ulcers were duodenal but the majority were gastric. The use of bone as a mechanical irritant increased the rapidity of the formation of the ulcers. The ulcers occurred after absorption of the drug and began with an initial destruction of the mucosal cells. Progression and healing were similar to that observed in other experimental studies of peptic ulcer and to that observed in cases of ulcer in man.

It was then thought advisable to apply some of the surgical and medical methods used in the treatment of peptic ulcer in man to the treatment of dogs with peptic ulcers which had been produced by the administration of cinchophen. But since chronic ulcers heal rapidly when the administration of cinchophen is discontinued, and complete healing has been noted as early as two weeks and as late as seven weeks thereafter, the healing process was too rapid to enable us to evaluate with any degree of certainty the effectiveness of any form of prophylactic treatment. It was then decided to determine the effect of prophylactic treatment of peptic ulcer while the animals were being given cinchophen.

The following medical agents seemed to be in most general use in the treatment of peptic ulcer in man and were therefore employed: (1) A diet of milk alone, (2) alkaline powders plus a milk diet, (3) mucin, (4) duodenal extract, and (5) histidine monohydrochloride. A bland diet was used in all cases. Since gastro-enterostomy is one of the most universally used surgical treatments for peptic ulcer, it was selected. In addition pyloric exclusion or partial gastric exclusion was performed in a number of cases primarily to determine whether or not a peptic ulcer produced by administration of cinchophen could be produced in the absence of free hydrochloric acid.

METHOD OF INVESTIGATION

Forty-five dogs with a range of average weight varying from 11 to 32 kg. were used in these studies. In every case the dogs were normal before the experiment began. All normal dogs can be considered not to have peptic ulcers as statistics have shown this to be true. The dogs were given the routine kennel care and the majority were fed a diet composed of cracker crumbs, ground horsemeat, and evaporated, skimmed milk. This diet was of a calculated weighed amount known to be sufficient to meet the caloric requirements of the dog. A capsule containing 2 gm. of cinchophen, unless otherwise mentioned, was given to each animal daily for the first four days of each week. On the last three days no cinchophen was given, but the usual diet and prophylactic treatment were continued.

Several animals were used in preliminary studies for standardization of the methods of treatment employed. These were not included in this report.

All surgical procedures were performed while the animals were under surgical narcosis induced by ether, and a careful aseptic technic was employed. All dogs killed were given a light ether anesthesia and were then bled from the femoral arteries. These and the dogs that died were examined completely. Careful gross and microscopic examination was made of all demonstrable lesions.

RESULTS OF MEDICAL TREATMENT

Milk therapy. Two dogs, averaging 14 kg. in weight, were given a diet composed wholly of evaporated skimmed milk with a small amount of corn syrup added for sweetening. Three feedings of an amount exceeding that which the dog would take were given daily. In this way some milk was constantly present for the dog to take. If the animal refused the milk it was given by stomach tube. Cinchophen was administered as mentioned before and the milk was given for thirty consecutive days.

The nutrition of these two animals remained excellent during this period. One dog gained 1 kg.; the other lost 1 kg. They were killed on the thirty-first day. In each case a gastric ulcer, which appeared much less severe both grossly and microscopically than

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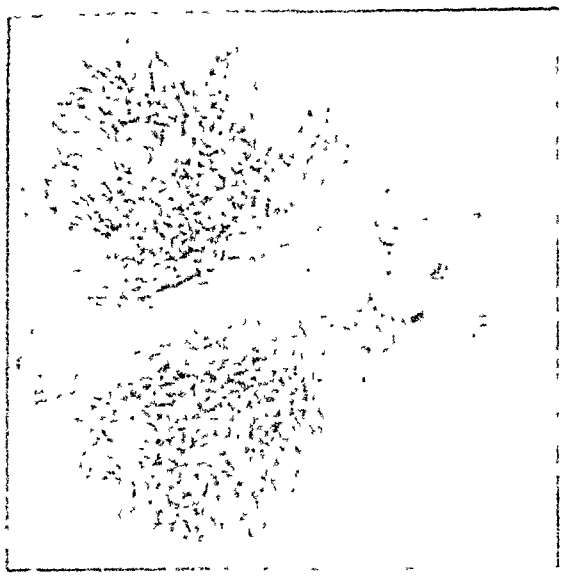


Fig. 1. Subacute ulcer on posterior wall of pylorus with surrounding mucosal erosions, gastritis, and a healed gastric ulcer on the posterior wall high in the pyloric antrum. This dog was treated with a diet of milk alone.

any of those seen in the control group (dogs given cinchophen but no prophylactic treatment) was found at necropsy. In one animal there was a completely healed gastric ulcer located on the lesser curvature and posterior wall of the stomach very near the pyloric ring. Just above this on the posterior wall, and also on the anterior wall directly opposite, was a small acute ulcer which involved the submucosa. In the other animal there was a small, subacute perforating pyloric ulcer located on the posterior wall. In addition, there were a few surrounding mucosal erosions, a slight degree of gastritis, and a completely healed ulcer high on the posterior wall of the pylorus (Fig. 1).

In comparison with the control animals, the animals receiving milk gave evidence of much less reaction from the cinchophen. The only clinical evidences that an ulcer was present were a few tarry diarrheal stools and vomiting. The gastritis, although to a lesser degree however appeared as soon in these cases, but the process seen at necropsy was definitely acute to subacute in contrast to the chronic process seen in animals which had received a more irritating diet. The ulcers were much smaller and gave more evidence of healing than is usually seen.

Alkaline powders plus milk diet. Five dogs averaging approximately 15 kg. in weight were given a modified Sippy treatment. An alkaline powder of bismuth subcarbonate (10 grains; 0.65 gm.) and magnesium oxide (4 grains; 0.24 gm.) was given at 8:00 and 11:30 a. m. and at 3:30 p. m. A powder of calcium carbonate (8 grains; 0.5 gm.) and sodium bicarbonate (6 grains; 0.4 gm.) was given at 10:00 a. m. and at 2:00 and 5:00 p. m. The 2 gm. capsule of cinchophen was given at 8:00 a. m. A pan of milk and syrup in excess of the amount desired was given at 9:00 a. m., 12:00 m. and 3:00 p. m.; in addition, a large pan of milk and syrup was left in the cage for the dog to take during the night if he so desired. The powders and milk were given daily. In none of these five cases did a chronic lesion develop although a chronic lesion did develop in every animal in the control group. Each of these five animals had the usual gastritis during the first two weeks, but in the majority this had entirely disappeared by the thirtieth day.

At necropsy, an entirely normal appearing stomach was found in two cases. In a third animal there was a small (2 mm.) mucosal erosion near the pyloric ring and on the lesser curvature (Fig. 2). In addition, there was a nearly healed erosion on the greater curvature. In the fourth animal a rather mild diffuse gastritis was present, with a few minute erosion but no actual ulcerations. The fifth dog had a relatively normal stomach, but a small, superficial, healing mucosal erosion was present on the posterior gastric wall. The nutritional status of these animals at the time of necropsy was excellent. Each animal had lost on an average of about 1 kg.

The clinical picture of gastritis, that is, the tarry stools and occasional vomiting, as has been said, developed as soon but to a less degree in the treated animals as in the untreated (control) animals. In no case were we able to produce much more than gastritis in any of the treated dogs. In no case did a sizeable acute ulcer develop and in none was a chronic lesion seen. The animals tolerated the alkaline therapy well.

Gastric mucin. Four dogs of an average weight of 21 kg. were given 12 to 15 gm. of gastric mucin mixed in milk at 8:00 and 11:00 a. m. and at 2:00 and 5:00 p. m. daily. Two grams of cinchophen was administered at 8:00 a. m. The regular diet in which an additional 15 gm. of mucin had been mixed was given at 9:00 a. m.

In two cases the stomach appeared entirely normal at necropsy. In the third case there was a large, chronic, perforated gastric ulcer on the posterior wall very near the pyloric ring. Perforation was through the gastrohepatic omentum with penetration into the substance of the liver. In the fourth animal a large chronic ulcer was found at necropsy on the posterior

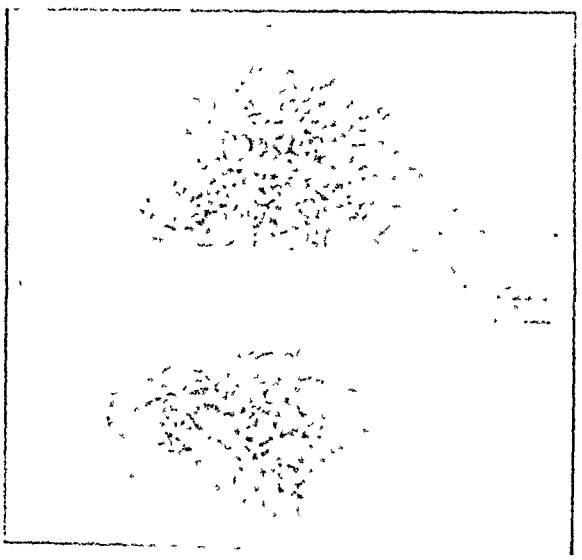


Fig. 2. Small mucosal erosion of the lesser curvature and nearly healed erosion of the greater curvature of the stomach of a dog treated with alkaline powders and a milk diet.

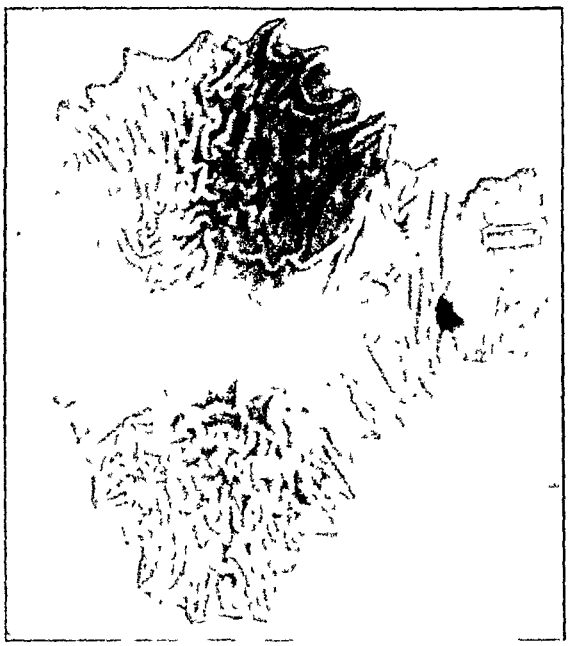


Fig. 3. Chronic ulcer on the posterior wall and lesser curvature of the stomach of a dog treated with gastric mucin.

wall of the lesser curvature near the pyloric ring (Fig. 3).

The symptoms of gastritis such as were seen in the control group developed in each animal receiving mucin. There was more diarrhea in this group, but grossly the amount of blood in the stool was much less. The animals' appetites were good for a longer period of time and there was less vomiting when mucin was given In no case was there any alteration in the nutritional state, and in general the animals given mucin were in a better state of nutrition than some of those in the other groups. Two of the dogs gained 2 kg ; the weights of the other two remained the same. The symptoms of peptic ulcer in the two animals in this group in which ulcer developed were less severe than in the control group.

These animals seemed to enjoy taking mucin and in most cases took it voluntarily. On a few occasions, however, it was necessary to administer it by means of stomach tube The two ulcers which developed were as severe as any in the control group, but in contrast there was no microscopic or gross evidence of damage to the stomachs of the other two animals in which lesions did not develop.

Histidine monohydrochloride. Four dogs were given a daily intramuscular injection of 5 c.c. of a 4 per cent solution of histidine monohydrochloride in addition to the bland diet previously mentioned. Two grams of cinchophen was administered four days of each week.

In none of these cases was any benefit observed as a result of the injections of histidine. A large, chronic peptic ulcer which was grossly and microscopically as severe as any seen in the control group developed in each of the four dogs (Fig. 4). Gastritis with clinical symptoms developed as early in these dogs and the symptoms of ulceration were as severe as in the control group. Their nutritional state was relatively unaltered, although three animals lost more than 1 kg. in weight. In every case the chronic ulcers were located in the pyloric region of the stomach on the lesser curvature and posterior wall. In one case the ulcer had perforated and there was an associated general peritonitis. No local or systemic reactions were noted from the injection of histidine.

We were unable to detect any alteration in the course of the development of the ulcer produced by cinchophen following injections of histidine.

Duodenal extract (2). Four dogs of an average weight of 21 kg. were given 150 grains (10 gm.) of duodenal extract daily. This was divided into three doses of 50 grains each and was given in capsules at 8:00 a. m., 12:00 m. and 4:00 p. m. Two grams of cinchophen were given at 8:30 a. m. for four days and the usual diet was given daily.

In every one of these cases there was some demonstrable lesion of the gastric mucosa, but in no case were these lesions as severe as those seen in the control group. No stomach was considered to be entirely negative, but one revealed only a rather mild diffuse gastritis with multiple small linear erosions. In the stomach of a second animal there were multiple, small acute ulcers, and a subacute ulcer about 1 cm. in diameter on the lesser curvature and posterior wall of the stomach near the pyloric ring (Fig. 5). The other two animals showed a rather diffuse gastritis with multiple mucosal erosions and small acute ulcers. In one of these there was a completely healed ulcer on the lesser curvature, and in the other there was much evidence of healing but no completely healed lesion. At necropsy an increased amount of mucus was found in the stomach of each of these four animals. The clinical symptoms of gastritis and ulceration appeared as early in this group as in the control group but were generally much less severe. The nutritional state of these four animals remained unaltered throughout the experiment.

These dogs were all somewhat larger than those used in the other groups, but chronic lesions developed

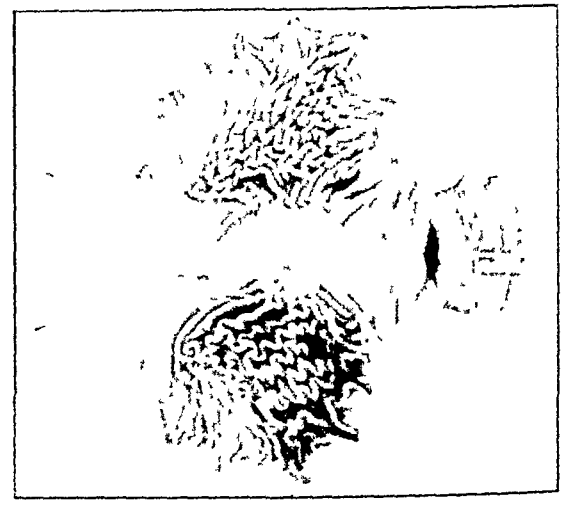


Fig. 4. Chronic ulcer on posterior wall and lesser curvature of stomach of a dog treated with histidine monohydrochloride. A similar type of ulceration was seen in the control animals.

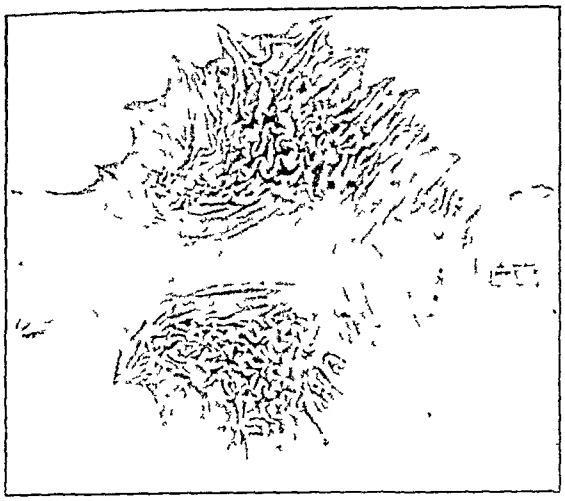


Fig. 5 Multiple acute and subacute ulcers in the stomach of a dog treated with duodenal extract.

in all animals of similar weight in the control group. The increase in mucus in these animals' stomachs seemed to be quite definite, although no actual measurement was made Frequently the appearance of the stomach at necropsy suggested that the animal had recently ingested a large amount of mucin. The toxic picture was about the same in these animals as in those receiving mucin; it was more severe than in those receiving the alkaline powders and milk diet, but was less severe than that presented by animals in the control group. It would seem possible that the action of the duodenal extract in these animals might have been brought about by an increase in the mucus secretion of the stomach, which in turn acted as a demulcent and prevented much of the acid erosion of the damaged mucosa.

CONTROL GROUP

Five dogs whose weight varied from 11 kg. to 31 kg. were used as controls. These were fed daily the usual diet of ground horse-meat, cracker meal, and evaporated milk and were given 2 gm of cinchophen four days of each week.

Two of the dogs died before the thirtieth day as a result of peritonitis from perforated gastric ulcer. The remaining three were killed on the thirty-first day. In one there was a chronic perforated ulcer on the lesser curvature, 1 5 cm. in diameter and approximately 2 cm. from the pyloric ring; in addition there were several contact ulcers, a large posterior wall ulcer in the cardia, and a diffuse mild gastritis with multiple erosions. A similarly severe picture was found at necropsy in the remaining two cases, a large, chronic gastric ulcer located on the lesser curvature and posterior wall near the pyloric ring being present in each.

Gastritis developed as usual from approximately the fifth to the twelfth day. The clinical symptoms were more severe in this group than in any treated group with the exception of those animals receiving injections of histidine, and no noticeable difference was noted between these two groups. In both these groups there was more vomiting, more pronounced tarry diarrhea, a greater degree of anemia and anorexia, and in general the animals appeared and acted sicker than in any of the other groups. In no case, however, was the nutritional state markedly altered, because the majority of the animals maintained their original weight.

RESULTS OF GASTROJEJUNOSTOMY

Anterior gastrojejunostomy was performed on five dogs whose average weight was 18 kg. This was done by anastomosing the jejunum to the greater curvature of the stomach with two and three rows of chromic catgut. Clamps were not used. The stoma was made about three times the diameter of the jejunum. The animals were allowed three to four weeks in which to recover from the operation and in every case were apparently in normal condition and had a perfectly functioning anastomosis before any experimental procedures were carried out. The usual diet was given daily in addition to 2 gm. of cinchophen, which was given on only four days of each week.

In each case the clinical symptoms of gastritis developed, but in no case was a gastric ulcer or gastrojejunal ulcer found at the time of necropsy. These symptoms of gastritis were usually as severe as in the control group, but at no time did they become as severe as those so frequently seen when an ulcer is present. The most outstanding symptom was anorexia, which developed about the fifteenth day. In these cases it was necessary to force feed in the animals. If this was done, food was usually retained and at the time of necropsy there was very little change in the nutritional state of the animals.

Two of the five dogs died as a result of pulmonary infection after the twentieth day of cinchophen administration; in each of these animals there was a mild gastritis with a few linear erosions, but no ulcer. The stomach, jejunum, and duodenum of two of the dogs that were killed on the thirty-first day appeared to be entirely normal. The jejunum and duodenum of



Fig. 6. Gastritis but no ulcer and a negative jejunum and duodenum in a dog on which gastrojejunostomy had been performed.



Fig. 7. Perforated chronic ulcer with multiple acute to subacute jejunal ulcers in the stomach of a dog subjected to pyloric exclusion. The excluded segment of a stomach to the right is negative, the dark discoloration being due to bile.

the fifth animal were negative, but marked gastritis with multiple mucosal erosions was present throughout the acid-secreting portion of the stomach (Fig. 6). The pyloric mucosa was entirely free from injury.

Posterior gastrojejunostomy is most frequently performed in man, but because of the ease of performance and a slight variation in anatomy, anterior gastro-enterostomy is usually performed in the dog. We feel that anterior gastro-enterostomy in the dog is equivalent to posterior gastro-enterostomy in man. At no time has it been necessary to perform entero-anastomosis. On a few occasions, in other experiments, a reversal of the afferent and efferent loops was done, but no differences could be noted.

THE ACID FACTOR IN THE PRODUCTION OF THE PEPTIC ULCER

We have previously shown that when an isolated pouch is made from the fundic portion of the stomach, a perforating peptic ulcer develops in the pouch when cinchophen is administered orally (3, 4). These ulcers form with greater rapidity than ulcers in the stomach proper. In the majority of such cases the ulcer perforated the wall of the pouch and peritonitis developed before there was much noticeable damage to the stomach proper. This was attributable to the fact that there was constantly some free hydrochloric acid present in the pouch. In addition, there was no alkalinizing mechanism, such as duodenal regurgitation, and emptying of the pouch was never complete.

The secretion of the pyloric portion of the stomach is slightly alkaline in contrast to the secretion of the rest of the stomach which is acid. More than 90 per cent of chronic ulcers produced by the administration of cinchophen are located in the pyloric region. It occurred to us that it might be possible to exclude this pyloric portion of the stomach and then administer cinchophen in an attempt to produce a peptic ulcer in the excluded segment. If no ulcer developed in this segment, a greater portion of the stomach, including part of the acid-secreting mucosa, could then be excluded in the same fashion. Cinchophen could then be administered to these dogs and, if an ulcer developed in the excluded portion of stomach, it might be said that the presence of free hydrochloric acid was essential for the development of peptic ulcers produced by cinchophen.

Anterior gastrojejunostomy was accordingly performed on sixteen dogs which varied in weight from 7 to 23 kg. This was done with the same technic as before, with the exception that the stoma in most cases was placed well above the pyloric portion of the stomach, and in a few cases was placed at the cardiac end of the stomach. The dog was allowed to recover completely from this operation and, when it appeared normal and had been eating its regular diet without distress for some time, a second operation was done. Exclusion of the entire pyloric portion of the stomach of eleven of the animals was then performed. This was done similar to the method of Devine (1925). In the remaining five animals approximately half of the entire stomach was excluded in a similar manner.

After three or more weeks in which to recover each of these animals was then given a daily dose of cinchophen and the usual diet.

The eleven dogs in which only the pyloric region had been excluded were given cinchophen in total amounts varying from 10 to 118 gm. over a period varying from five to 114 days. The average period was forty days, with the average total dose being 61 gm. of cinchophen.

There was no gross or microscopic evidence of injury to the excluded pyloric segment of the stomach of these eleven dogs. In four instances a jejunal ulcer was located on the posterior wall of the efferent loop of jejunum, near the gastro-enteric stoma, and in one of these cases the jejunal ulcer had perforated and the dog had died from generalized peritonitis (Fig. 7). The other seven dogs showed no evidence of jejunal ulcer. In ten of the animals there was definite gross and microscopic evidence of gastritis and small mucosal erosions diffusely scattered throughout the stomach. The eleventh animal in this group showed no damage to the gastric mucosa. In no case was a definite gastric ulcer present.



Fig. 8. Two acute ulcers and gastritis in the excluded segment of stomach.

In every case these eleven animals manifested symptoms of gastritis in the usual period of time. At necropsy this gastritis varied from a mild to a rather severe degree, but in the majority of instances the gastric mucosa was slightly edematous, with multiple linear erosions containing small blood clots and, in a few cases, small mucosal ulcerations.

The five animals in which nearly half the stomach had been excluded were given cinchophen in doses varying from 1 to 2 gm. daily for a period varying from six to forty-eight days, an average total period of twenty-three days elapsing and 25 gm. of the drug being the average total dose. Jejunal ulcer developed in three of these animals. These ulcers were in the same location as the jejunal ulcers in the previous group. In two instances the jejunal ulcer had perforated and the animals died from general peritonitis. The remaining two animals which did not have jejunal ulcers, died as a result of toxemia.

In all five instances there was gastritis similar to that described, but, in addition, the major process was in the excluded segment of the stomach. In one animal there was a definite gastritis in this excluded segment with two acute ulcers, 1 cm. in diameter, on the posterior wall in the pyloric mucosa close to its junction with the acid-secreting mucosa (Fig. 8). In another animal there was a large amount of bloody material in the duodenal loop, with diffuse gastritis of the excluded stomach. There were multiple erosions and small ulcerations throughout this entire segment. The excluded portion of the stomach of a third animal was filled with blood clots. There was diffuse gastritis of the entire mucosa with several small acute ulcers in both the pyloric and fundic mucosa of this segment. In contrast, the stomach proper showed only a mild gastritis. No jejunal ulcer was present. The other two animals' stomachs demonstrated similar pictures, and in both cases there was marked gastritis with an associated acute ulcerative condition in the excluded segment.

In the majority of these cases in which some surgical procedure was carried out gastritis developed within the expected period of time. In no case, however, was a true peptic ulcer produced in the stomach or duodenum following any of these procedures. In seven of the sixteen animals (43.7 per cent) in which an exclusion operation was performed a jejunal ulcer developed, but a jejunal lesion did not develop in any of the animals in which only gastrojejunostomy had been performed.

The symptoms presented by the animals when a jejunal ulcer developed were the same, but to a more severe degree, as those present when a gastro-duodenal ulcer develops. The fact that in all of the animals in which some of the acid-secreting mucosa was excluded, definite ulcerative damage of the excluded mucosa developed would suggest that free hydrochloric acid is essential for the development of peptic ulcers produced by cinchophen. The ulcers which did develop in the excluded segment of the stomach were always acute to subacute and were much less severe than those that developed in unaltered stomachs. This may be due to the lesser degree of mechanical irritation to the isolated portion of the stomach.

SUMMARY AND CONCLUSIONS

Some benefit was found from a diet of milk alone and from the use of a duodenal extract in the prophylactic treatment of peptic ulcers produced experimentally by the administration of cinchophen. Mucin appeared to be definitely beneficial in some cases but in others a chronic ulcer developed similar to those found in control animals fed cinchophen without prophylactic treatment. A chronic lesion was not produced in the presence of alkali-milk diet therapy. No benefit was observed from intramuscular injections of histidine monohydrochloride.

In none of the animals subjected to gastro-enterostomy did gastric, duodenal, or jejunal ulcers develop. A jejunal ulcer frequently developed, however, when pyloric or gastric exclusion had been performed. No lesions were observed in the isolated pyloric segment of the stomach, although definite ulceration occurred when acid-secreting mucosa was included in the isolated portion of the stomach.

From these observations and from studies of gastric secretion it would appear that gastric acidity is a factor in the experimental production of peptic ulcers by administration of cinchophen.

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SECTION III—*Nutrition*

The Effect of Vitamin D on Intestinal Atony of Rickets*

By

LESTER YODER, M.S.

AMES, IOWA

IN previous reports (1) from this laboratory on studies of the action of vitamin D it was stated that intestinal reduction of iron in deficient animals was decreased by feeding vitamin D and that the surface tension of the intestinal juice was also decreased by calcifying doses of the vitamin. It appeared as if these effects probably could be brought about by any treatment which would decrease the time required for the passage of food through the digestive tract because a sharp temporary decrease of reduced iron in the feces of rachitic rats could be brought about by feeding effective doses of certain purgatives. This was consistent with the reports of Menville, Ane and Blackberg (2, 3), who, through the use of barium test meals and the roentgenoscope, found a decreased motility in parts of the gastro-intestinal tracts of rachitic rats. By a similar technique Harris and Bunker (4) found more recently that vitamin D deficient rations caused hypomotility in all parts of the gastro-intestinal tracts of rats and that supplements of the vitamin brought about greater motility. In this laboratory similar conclusions were reached by employing a different technique in an effort to determine the reason for the sudden change in intestinal pH and iron reduction produced in rats whenever a rachitogenic ration was supplemented with effective doses of vitamin D.

Young rats made rachitic by subsistence on the Steenbock ration 2965 were placed in individual cages and used in some comparisons between animals which were fed vitamin D and their litter mates which were not fed the vitamin. Vitamin D was added to the rachitogenic ration of representative rats of each of five litters in the form of Viosterol dissolved in carbon tetrachloride. After at least six days of vitamin therapy one per cent of lamp black was incorporated in the ration of both the deficient and the vitamin treated rats. After the rats had fasted for several hours the carbon ration was fed in portions at the rate of 2 g. per rat at intervals not to exceed the ordinary rate of consumption of the feed. The time of the first feeding of the carbon ration was noted and thereafter the time of the first appearance of black feces.

The Viosterol consumed varied from 2.2 mg. to 8.8 mg. per rat. From tests with many other rachitic rats 2.2 mg. of this preparation of Viosterol barely produced a narrow continuous line of calcification.

The data in Table I show one case in litter 90 where one of the 7 rats receiving the vitamin required slightly more time for the passage of the carbon than any of its rachitic litter mates. This rat would not eat regularly. In other experiments with vitamin D it was found that some animals finally refused to eat

TABLE I

Effect of the ingestion of Viosterol upon the time required for the passage of food through the digestive tracts of rachitic rats

Litter No.	Viosterol consumed per rat	Rat No.	Time hrs.	Average % decrease due to Viosterol
54	2.2 mg. in 7 da.	449	8.5	30
	None	445 446 447 448	11.4 12.4 10.2 14.8	
55	2.2 mg. in 7 da.	451	7.6	26
	None	452 453 454 455	11.7 9.25 9.75 10.75	
89	2.8 mg. in 10 da.	471	9.5	37
	None	467 469	15.5 14.5	
90	2.9 mg. in 10 da.	472 473	11.7 14.0	9
	None	475 476 477	14.0 15.0 13.5	
312	8.8 mg. in 8 da.	500 501	11.75 10.5	30
	None	502 503 504 505	14.25 16.25 14.5 16.75	

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the ration at the usual rate. Nevertheless, the average decrease per litter in time required for the passage of food through the digestive tracts of the rats due to the ingestion of the small amounts of vitamin D was 26 per cent. Since the larger additions of vitamin D to the animals of litter 312 did not induce a proportionate decrease in the time required for passage of the carbon, it seems there must be a minimal requirement of vitamin D by the digestive tract for a tonicity which can maintain either a decreased intestinal volume or increased motility. Thus, shorter digestion periods induced by the ingestion of vitamin D may account for the accompanying decreases in the intestinal reduction of iron.

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The Effect of Vitamin D on Intestinal Iron Reduction*

By

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IN feeding experiments with rachitic rats it was noted in this laboratory that vitamin D caused iron supplements to the rations to pass through the digestive tracts of the animals in a less reduced state. A reason for this action of the vitamin was recognized when it was found in this laboratory also that small amounts of vitamin D caused a significant decrease in the time required for the passage of food through the digestive tracts of rachitic rats (1). Apparently such a change in rate of passage of food prevents a rise in intestinal reduction intensities of sufficient magnitude to bring about the conversion of ferric iron to the ferrous state. The effect proved to be so general and so marked that the possibility of its use as a test for vitamin D was also investigated.

Due to the relation of oxidation-reduction and acid-base systems such a test probably would be a corollary of the decrease induced in the pH of the feces of rachitic rats following the ingestion of vitamin D. This effect on fecal pH was observed by Zucker and Matzner (2) who proposed and patented it as a test for vitamin D. That oxidation-reduction systems and acid-base systems are intimately related was shown by the physico-chemical researches of Clark and coworkers (3).

Bergeim (4, 5) published a method for the evaluation of intestinal putrefaction which involved the addition of a small amount of hydrated ferric oxide to the ration and a subsequent estimation of the ratio of reduced to total iron appearing in the feces. He used this ratio as an index in a study of the effect of various constituents of a ration on intestinal reduction and putrefaction.

In the work herein reported Bergeim's index of putrefaction or reduced iron determination was used in studying the effect of vitamin D upon intestinal reduction in rats. For purposes of comparison as criteria for ingested vitamin D parallel determinations of fecal pH and tests for bone calcification were also included.

METHODS AND RESULTS

Determination of reduced iron. As little as 0.05 gm. of intestinal residuum or feces was macerated in a short test tube 18 mm. in diameter with 6 c.c. of 12 per cent hydrochloric acid and heated in a boiling water bath for 40 seconds. The solution was then

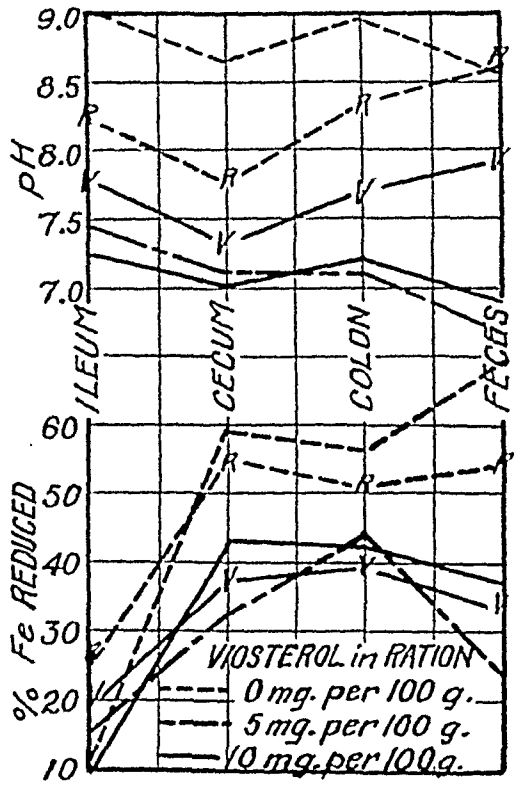


Fig. 1. Effect of vitamin D upon iron reduction and pH in the lower digestive tract of rats.

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Submitted September 29, 1936.

filtered through a long-necked funnel previously fitted with rapid filtering ash free 7 cm. filter paper. Two c.c. of the filtrate were pipetted into each of two 25 c.c. graduated cylinders. To one was added dropwise about 0.05 N potassium permanganate solution until the color no longer disappeared immediately. Usually 3 to 5 drops were required. Then to each cylinder were added 2 c.c. of 2 per cent potassium thiocyanate solution and enough distilled water to bring each to the same volume suitable for comparison in a colorimeter. The lower reading of the solution oxidized with permanganate divided by the higher reading of the unoxidized, multiplied by 100 and subtracted from 100 gave the per cent of the total iron which was reduced. This is Bergeim's index of reduction. The procedure gave for the unfed rachitogenic ration 1.0 per cent and for the same ration containing added vitamin 2.3 per cent of reduced iron.

pH was determined potentiometrically with the quinhydrone electrode and the saturated calomel electrode cell and corrected to 25° C.

The vitamin effect on intestinal reduced iron. Six litter-mate rats which had become rachitic on the vitamin D deficient ration were placed in groups of two each and fed, respectively, 0, 5 and 10 mg. of Viosterol per 100 gm. of the ration over a period of 20 to 30 days. They were then posted one at a time and the contents of the ileum, cecum and colon of each animal removed to determine immediately the pH and per cent of reduced iron. The results were averaged for each group and are shown in Fig. 1.

Four rachitic rats of another litter were divided into two groups, one of which was fed Viosterol at the rate of 10 mg. per 100 gm. of the deficient ration for only 3 days. These were then posted and the contents of the lower tracts likewise examined. The averaged results are shown on the diagram of Fig. 1 as lettered graphs, R and V.

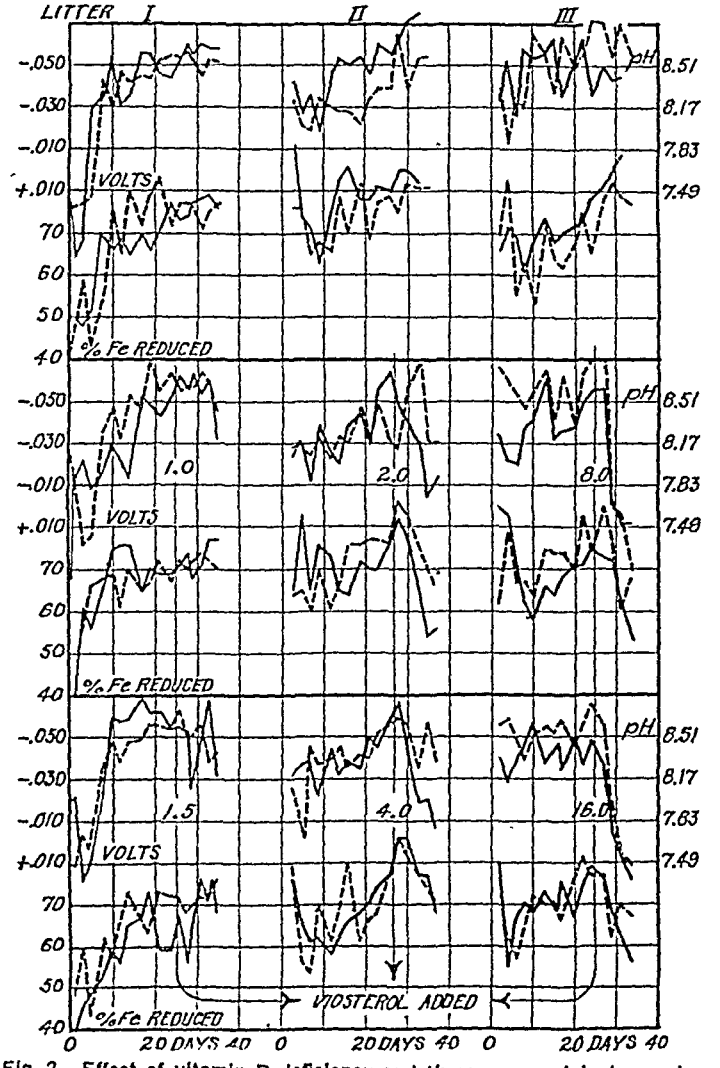


Fig. 2. Effect of vitamin D deficiency and therapy on quinhydrone electrode potentials and reduced iron in the feces of rachitic rats.

The results show that intestinal iron reduction rose from a small value in the ileum to relatively large values in the cecum and lower portions of the intestinal tracts of rachitic rats. Ingested vitamin D had little if any effect on iron reduction in the ileum but definitely brought about decreased reduction in the cecum, colon and feces. This decrease was the greatest in the feces. That 10 mg. of the Viosterol apparently produced a smaller decrease in intestinal iron reduction than 5 mg. is accounted for by the fact that this effect of the vitamin, after an extended treatment such as this, is not constant.

The vitamin effect on fecal reduced iron. In order to find the effect of the deficiency disease and its treatment with vitamin D upon the iron content of an ingested deficient ration it was desirable to determine the per cent of reduced iron in the feces of standard rachitic rats during incipient rickets and during treatment with various doses of vitamin. Sufficiently large doses of vitamin D would cause a "break" downward in a rising curve of per cent of fecal reduced iron. The rats could then be "line-tested" for bone calcification as usual and a comparison made of the relative minimum effective doses of vitamin necessary to cause a break in the reduced iron curve or a positive calcification in the "line" test.

Not only determinations of reduced iron but also determinations of quinhydrone electrode potentials were made on every sample of feces obtained throughout the test period. Graphs from the data, being the same as for the fecal pH change effect, were then directly comparable.

Changes in fecal reduced iron were studied in growing rats during the entire period of subsistence on the Steenbock and Black ration 2965 modified to contain 0.5 per cent of powdered hydrated ferric oxide. The animals weighed about 60 gm. when weaned and started on the rickets producing ration. All animals in each comparison were fed the same amount of ration in individual wire bottom cages. All tests were made on fresh feces obtained by digital pressure on the colon of the rats. Representative comparisons were made from 18 rats or three litters, I, II and III, of six rats each. From one to three days after the animals were started on the rachitogenic ration samples of feces were examined at once for effect on quinhydrone electrode potential and for ratio of reduced to total iron according to the methods already described. This routine was repeated every other day except Sundays on all rats until the experiment was terminated on the tenth day following the first additions of vitamin D to the diet. The experimental data were thus obtained over a period of 34 to 37 days. Two rats of each litter were fed no vitamin and the other pairs of rats were fed the vitamin in the form of Viosterol in doses of 1.0, 1.5, 2.0, 4.0, 8.0 and 16 mg. per 100 gm. of ration, respectively, beginning on the 25th or 27th day of subsistence on the rachitogenic ration. The Viosterol was a commercial 100 D preparation which, however, had a lower potency at the time it was used in these experiments.

The data are shown in the form of a graph for each animal in Figure 2. Since the voltage of the cell, composed of the quinhydrone and saturated calomel electrodes, bears a linear relation to pH, the graphs would be the same for both voltage and pH. The graphs show true changes in voltage or pH but actual changes in alkalinity were minimized by the graphs when high and exaggerated when low. However, it should be borne in mind that the values rose from a low alkalinity to a higher alkalinity as the deficiency disease progressed in the rats.

Iron reduction variations were similar to variations in pH and showed a rise from low percentage reduction to higher more constant values as rickets progressed.

As the dose of vitamin was progressively increased no "breaks" in these graphs due to the addition of Viosterol were noticeable until 2 mg. per 100 gm. of ration were administered. Then the pH or voltage graphs and iron reduction graphs both recorded the effects of vitamin in the ration. There was probably some effect recorded at the 1.5 mg. level by the pH or voltage graph. Increased dosage did not alter the nature of the "break" much; it merely occurred sooner.

Although the graphs clearly show the presence of vitamin D in the diet at 2 and 4 mg. levels, there was no evidence of calcification in the rachitic bones of these animals. The 8 mg. dose gave a narrow continuous "line" and 16 mg. a wider line of calcification. The changes in fecal iron reduction are quite generally of this nature as the application of such graphs to tests with many other rats has shown. The decrease in fecal reduced iron has also been produced with additions of irradiated ergosterol to the ration. Unirradiated ergosterol has no effect. Therefore it is a characteristic effect of vitamin D.

SUMMARY

By determinations of reduced iron in the feces and in various parts of the intestinal tracts of rachitic rats it was found that ingested vitamin D caused a distinct decrease in a high intestinal iron reduction characteristic of a rachitogenic ration containing added iron.

Determinations of reduced iron in the feces of rats during the onset of rickets and during vitamin D therapy gave variations similar to variations in pH. As supplements of the vitamin were increased from ineffective amounts it was found that sharp decreases in fecal reduced iron occurred before calcification.

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SECTION IV—*Roentgenology*

The Importance of Preliminary Films in a Routine Examination of the Abdomen*

By

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PRELIMINARY films of the abdomen are a necessary aid in diagnosis, for they may show conditions which are not evident clinically. They may also confirm an uncertain diagnosis as well as assist greatly in determining acute conditions. Indeed, just as at the first sign of trouble in the thorax of a patient, chest films are taken as an efficient method of aiding the diagnosis, so preliminary films of an abdomen ought to be made as a routine procedure on a patient who gives a history of an abdominal complaint.

In effect, medical literature does offer certain references which have already pointed out the value of this procedure. However, most of this literature, which refers to preliminary films in diagnostic work, relates directly to one condition or another in which this procedure is helpful, for example, intestinal obstruction, echinococcus cysts, etc. Two books, recently published, discuss this subject in general (1). Still, there remains a vacuum in medical literature relative to preliminary films in all their possibilities in the diagnosis of abdominal disorders. It is our aim, therefore, to synthesize the research already available on preliminary films in reference to only one condition or system and to offer a generalized view of the subject as well as to stress the value of this method as a routine procedure.

Great emphasis has been placed on the use of preliminary films in diagnosing acute abdominal conditions. Their assistance in these conditions is so important that most of the literature dealing with the subject of preliminary films is in reference to acute conditions. For example, Singer has published a series of articles, which stress this point. He writes that "in connection with acute abdominal emergencies the roentgen ray finds its greatest field of usefulness in perforated ulcers" (2). Kraas makes a similar comment on preliminary films as they are used in cases of intestinal obstruction. "*In jedem Fall von zweifelhaftem oder ungeklärtem Ileus möchte eine Röntgenplatten Aufnahme ohne Kontrastmittel, womöglich in stehender Stellung, ausgeführt werden*" (3). These two opinions, selected from many similar statements, may serve to make clear that the use of preliminary films, taken in prone, erect and lateral views, in acute abdominal emergencies are of unmistakable diagnostic importance.

Moreover, as we have stated, preliminary films are of equal importance in correcting a faulty clinical diagnosis of abdominal conditions.

Thus:

Mr. M., a man of 55 years of age, was referred to us for a roentgen examination of his spine. He had been

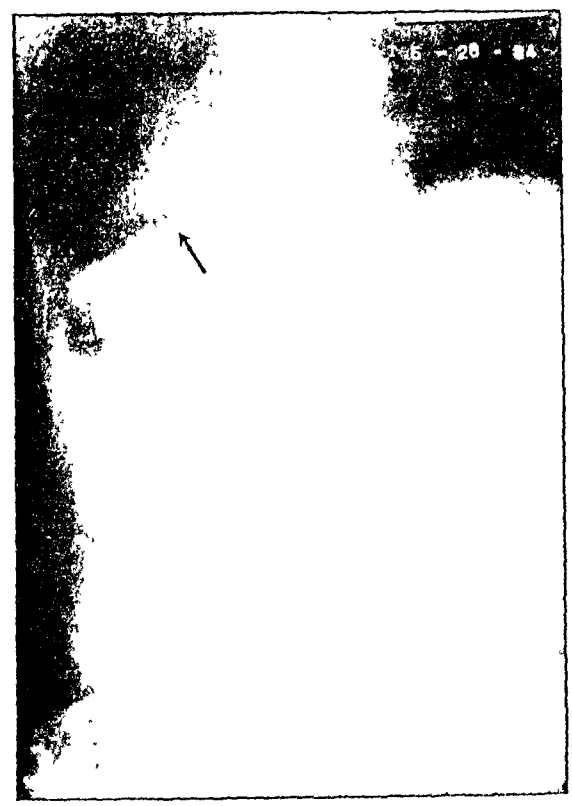


Plate 1. Film showing air under the diaphragm; result of perforated duodenal ulcer.

*From the X-ray service of Dr. George Plehn, City Hospital, New York City.
Received March 27, 1926.

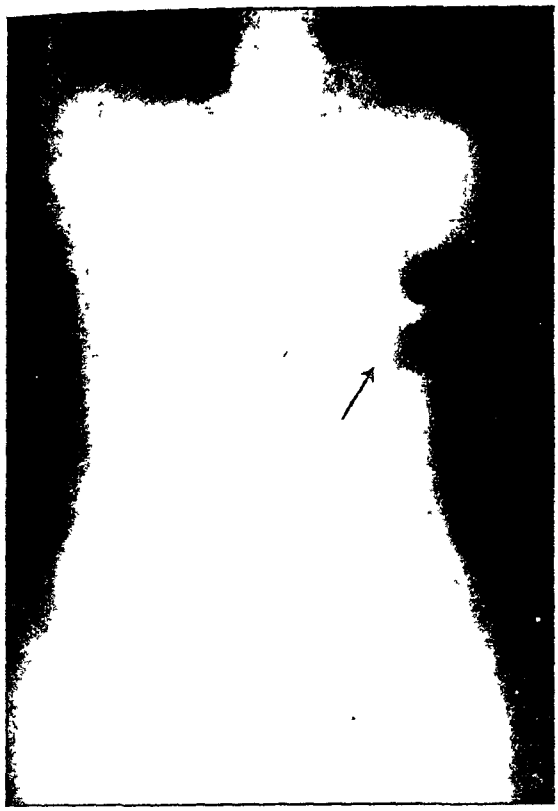


Plate 2. Film showing small bowel distension; result of intestinal obstruction.

complaining of a severe backache that lasted for some weeks. A preliminary film showed that an enlarged prostate, which had previously been diagnosed as benign hypertrophy, was malignant as there was a metastasis to his spine. Later findings confirmed this diagnosis.

Not only in acute abdominal conditions and in correcting a faulty diagnosis, as in the case we mentioned, are preliminary films found to be useful. They may also show conditions which are not at the time evident clinically.

In a roentgen examination, which was made of Mr. T., a man of over 40 years of age, who had sprained his back, we were able to note an adrenal tumor which had given no clinical evidence of its presence. It is certain, then, that the value of preliminary films of the abdomen as a triple aid to diagnosis is vital in various conditions.

These various conditions, which may be seen and diagnosed both as to their nature and location often in preliminary films, taken in various positions, may be briefly enumerated by us. We shall begin with conditions of the gastro-intestinal tract. Perforated ulcers may very often be diagnosed in preliminary films. Medical literature contains some references to this subject (4). We shall, therefore, add only a report of a case as an illustration.

Mrs. M., age 42, had a pain in her abdomen for seven hours. The pain was associated with retching and vomiting. It was very severe and sharp. There was no history of previous attacks. A clinical examination showed a rigid abdomen with a marked rebound tenderness. A preliminary film study revealed that there was air between the liver and diaphragm, a condition which is characteristic of a perforated ulcer in the gastro-intestinal tract. The patient was operated on immediately. The findings were a perforated duodenal ulcer.

The preliminary film is of equal importance in the diagnosis of intestinal obstruction. Ginsberg points out that preliminary films differentiate between a small and large bowel obstruction by showing the location of the lesion since small bowel obstructions are feathered, serrated and ribbed in appearance due to the valvulae conneventes, while large bowel obstructions are blunted and there are deeper indentations due to haustrations. Preliminary films of the intestines, then, may show not only an obstruction but its site as well (5). There is a large volume of medical literature which deals with this subject (6). We shall cite, nevertheless, a case to illustrate the use of a preliminary film study in this condition.

Mrs. K., age 44, was troubled for three days with nausea, constipation and pain in the abdomen. She had no relief from enemas. On examination her abdomen was not rigid; however, it was tender, and there was visible peristalsis over the right lower quadrant near an old scar. A preliminary film study showed air in the small bowel with a fluid level. The operation disclosed a small bowel obstruction caused by adhesions to an old appendiceal scar.

In the diagnosis of gall bladder and liver conditions, a preliminary film may also be of service. Hydrops of the gall bladder, calcified gall bladder, calculi, calcified liver abscess, and subphaenic abscess may be noted occasionally in a preliminary film study. Dr.

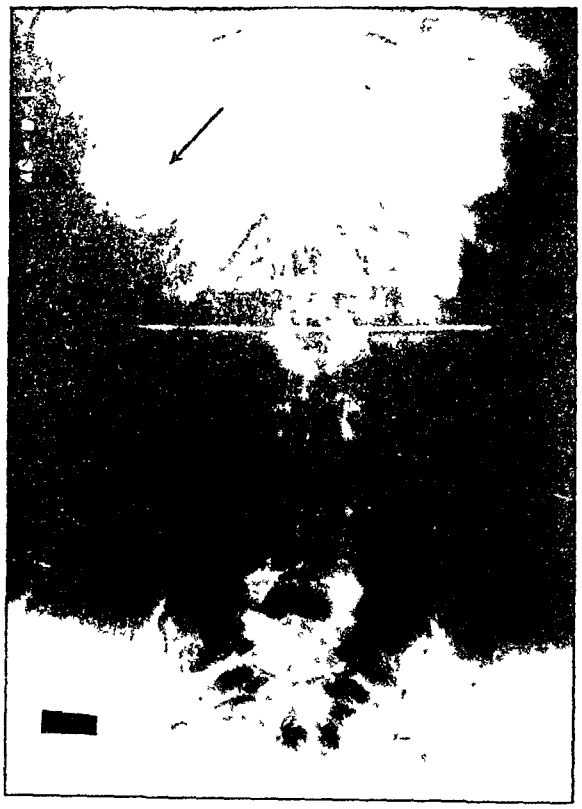


Plate 3. Film showing gall bladder calculi.

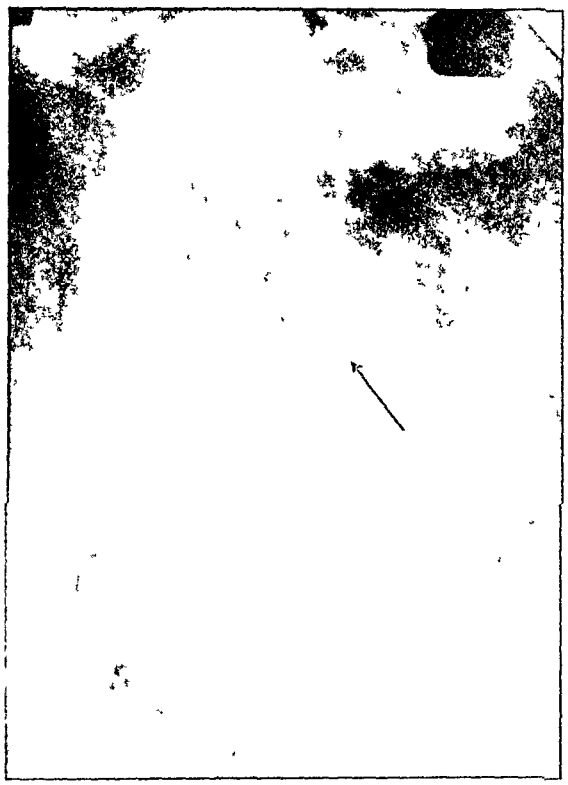


Plate 4. Film showing ectopic kidney with calculi.

Arnold described in an article how an echinoccocus cyst of the liver may be disagnosed either from indirect evidence, such as the displacement of adjacent organs, and occasionally, from direct evidence produced by the calcification of the cyst by the use of roentgenography (7). Gall stones may also show up on a preliminary film study without the use of a dye as in the following case.

Mrs. S., age 51, two weeks previous to our examination, was troubled by a sticky, scratchy pain in the left upper quadrant. She was treated at Harlem Hospital for pylonephritis. Later, she was transferred to City Hospital. An examination showed no masses or rigidity. However, there was tenderness in the right upper quadrant anteriorly and posteriorly. A preliminary film study revealed stones in the gall bladder. An operation confirmed the diagnosis.

In conditions of the urinary tract a preliminary film may also be of assistance. Such conditions as a stone in the kidney, bladder, calculus, a stone in the ureter, an ectopic kidney, peri-nephritic abscess, tumors of the kidney, polycystic kidneys and tuberculous or calcified kidneys may often be noted in a preliminary film These cases are useful as illustrations

Mrs. C., age 25, who had been delivered thirteen months previously of her first baby, was told at the hospital ten months ago that she had a tumor in the lower abdomen which was probably an ovarian cyst. However, this quasi-tumor gave rise to bilious attacks every two weeks with pain in the left side brought on by exertion. An examination showed a globular mass in the left lower quadrant which extended to the umbilicus. A vaginal examination showed that the mass did not extend into the left fornix. A flat film was made and revealed an ectopic kidney with a dendritic calculus in the pelvis. An operation confirmed these findings.

Mr. H., age 41, complained of pain, which had come on suddenly, in the right upper abdomen. The pain was intermittent and referred to the right thigh. It was followed by nausea and vomiting but he had no fever. An examination showed no masses, no tenderness and no spasms. A flat film revealed a stone on the right side. An operation gave evidence of a stone in the ureter.

Mrs. T., age 31, complained of a dull, aching pain at the right side below the costal margin. She had suffered nausea, vomiting and hematuria for a week. An examination of the patient, who was very obese, showed no tenderness on deep pressure in the right lumbar area. There were no masses felt. Her temperature was 102 degrees. A preliminary film revealed that the left kidney was normal, the right kidney markedly enlarged and its shadows were very irregular. There was complete obscuring of the psoas muscular markings on the right side. An operation showed an extensive peri-nephritic abscess.

In addition to the conditions, which we have listed above, preliminary films show the following: for example, enlarged spleen, in gynecological conditions, calcified fibroids, ovarian cysts and dermoid cysts; in obstetrics, for studies of the pelvic structure (8), abnormal pregnancies and multiple pregnancies as well as for normal pregnancies. And finally, to complete the list we must include the skeleton and its anomalies in reference to abdominal conditions, tuberculous bones, syphilitic bones, Paget's disease and primary and secondary malignancies and foreign bodies.

The technique of the preliminary film in relation to foreign bodies is of special aid since patients are often unable to remember or do not know that they have

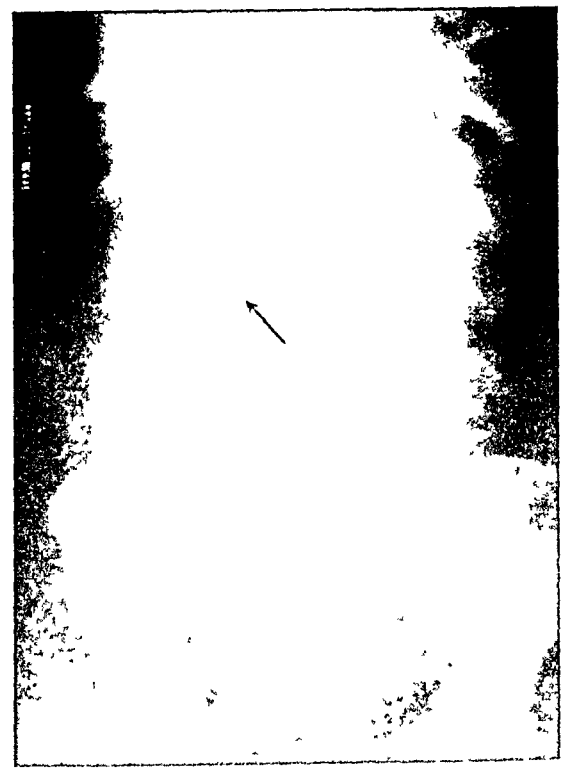


Plate 5. Film showing obscuring of psoas musculature.



Plate 6. Film showing foreign bodies.

swallowed a foreign body and their symptoms are not explicable clinically. However, preliminary films may often show the cause of the discomfort and its location as in the following case:

Miss H., age 11, a psychotic, was admitted to the hospital. She was complaining of a vaginal discharge. One month later she was bothered by pain in the right lower quadrant. This pain was accompanied by vomiting and loss of appetite. An X-ray examination revealed two safety pins and a common pin in her intestines.

SUMMARY

This brief outline of the preliminary film in reference to various conditions of the abdomen may serve to point out the intrinsic value of this procedure in diagnostic work. The preliminary film procedure is simple, without discomfort to the patient, and is a definite aid in diagnosing abdominal conditions which are not evident clinically. It may also serve as a means of controlling a faulty diagnosis and it can assist in designating the site of acute conditions. Because of this triple function of the preliminary film procedure, it is to be recommended as a routine procedure in all cases of abdominal complaints.

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Carcinoma of the Tail and Body of the Pancreas

A Roentgenologic Technique for Its Demonstration

By

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THE purpose of this communication is to describe a roentgenologic maneuver which is useful in demonstrating a tumor of the tail and body of the pancreas. The nature of the tumor, whether it be benign or malignant, can then be determined by the patient's clinical picture. In order to illustrate the usefulness of this roentgenologic procedure, a case is cited in which the diagnosis of carcinoma of the tail and body of the pancreas was established through its application. This example stresses the aid contributed by such X-ray information, since the recognition of carcinoma of this portion of the pancreas is only seldom accomplished prior to exploratory laparotomy or necropsy.

The pancreas does not lend itself to X-ray exami-

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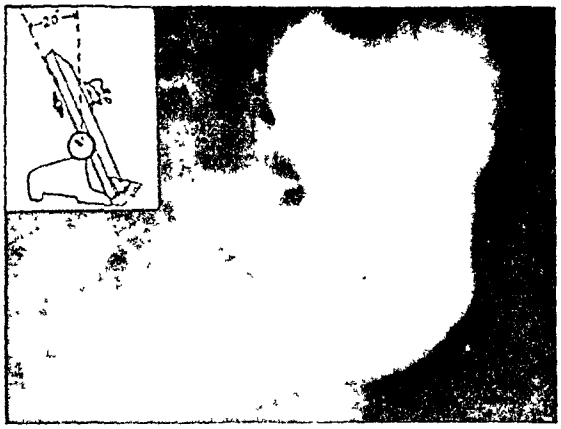


Fig. 1. The filling defect near the lesser curvature of the stomach is produced by the retrogastric mass. This film was made with the patient lying prone on the tilt-table, inclined to about 20 degrees from the vertical.

nation. Its specific density is not much different from that of the surrounding tissues; neither is there any suitable roentgen contrast material applicable to this organ. For these reasons, the gland cannot be directly roentgenographed. Perhaps, as by the injection of colloidal thorium salts the liver and spleen have been visualized, so too, some day a method may be discovered for rendering the pancreas radiographically opaque. But so far, its form may be studied by indirect means only. It can be recognized by such pressure changes as the pancreas exerts upon the neighboring stomach, duodenum, or colon, which, in turn, can be readily photographed by filling them with suitable contrast media.

There are three indirect roentgenologic signs of tumor of the pancreas. The first of these is the expansion of the shadow of the horse-shoe curve of the duodenum. Carthy (1) explained this as the result of tumefaction of the head of the pancreas, for it is in close relationship to the mesial surface of the curve of the duodenum. Carcinoma in this region, by its increasing size, presses back the duodenum and not only widens the "C" curve which the bowel normally assumes, but may even compress it. Gutman and Jahiel (2) testified to the value of this indirect sign and illustrated it by reporting their case of carcinoma of the head of the pancreas, which produced a widening of the duodenal curve and, in addition, showed invasion and stenosis of the duodenum.

Such obstruction of the duodenum is the second indirect roentgenologic sign of tumor of the pancreas. This obstruction or partial stenosis need not be limited to the portion of the duodenum lying close to the head of the pancreas. It may occur in the distal part of the duodenum, as well, if the tumor springs from the adjacent body of the pancreas. The case reported by Vorhaus (3) exemplifies such obstruction of the third part of the duodenum, due to carcinoma of the body of the pancreas.

The third indirect sign is that of extrinsic pressure exerted by a tumor of the pancreas upon the adjacent portion of the stomach. Such a filling defect of the stomach has frequently led to the erroneous diagnosis of gastric malignancy. The instances reported by Scholz (4, 5) are examples. Because of the irregular filling defect on the greater curvature, he diagnosed carcinoma of the stomach in each of his three cases. But postmortem examination showed that this filling defect had been produced by extrinsic pressure and by adhesions of the stomach to a carcinoma of the tail of the pancreas.

The pressure of the pancreatic neoplasm may not bring about a constant filling defect of the margin of the stomach. Instead, it may press upon the body of the stomach and distort it. In the case to be described, no such encroachment upon the stomach was observed when the patient was standing erect in front of the fluoroscope. Only when some pressure was applied to the anterior abdominal wall was there elicited any sign of a retrogastric tumor. Similarly, when the patient was bent backwards by partially lowering the fluoroscopic tilt-table, there was seen a filling defect of the body of the stomach, produced by the tumor in the pancreas. This observation suggested the following roentgenographic technique to demonstrate the presence of a mass behind the stomach.

RADIOGRAPHIC TECHNIQUE

The patient, after ingesting the usual barium meal, is placed erect against the vertically tilted X-ray table, his abdomen against the table top. Under direct fluoroscopic control, the table is gradually lowered until a point is reached where the stomach is pressed upon by the structures lying behind it. These are the spine, the abdominal aorta, and the body of the pancreas. Normally, no filling defect of the body of the stomach is noted until the table is tilted nearly to its horizontal position. Then one frequently sees the familiar localized compression of the middle of the stomach as it crosses the shadow of the lumbar spine. But when there is present a retrogastric tumor such as carcinoma of the body of the pancreas, then the filling defect of the stomach becomes noticeable much sooner. Figure 1 shows the degree of pressure on the stomach obtained by titling the X-ray table about twenty degrees from the vertical. At this angle, only a small filling defect is seen above the incisura angularis. When the table is lowered to about forty-five degrees, the stomach is more extensively compressed by the tumor of the pancreas behind it, as shown in Figure 2. Now, the filling defect extends trans-

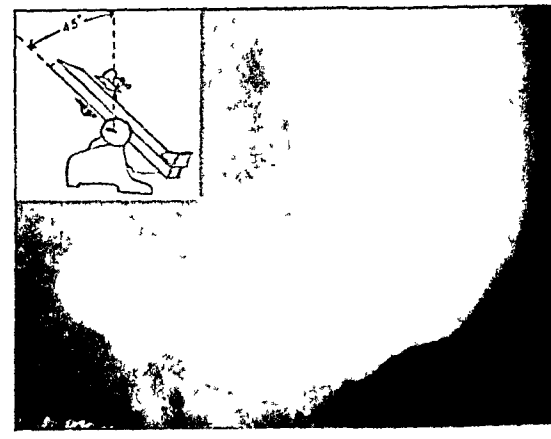


Fig. 2. With the tilt-table inclined to about 45 degrees from the vertical, the retrogastric mass now produces a filling defect of the stomach representing an area of compression extending towards the pylorus. Its form and location suggest a tumor of the tail and body of the pancreas.



Fig. 3. Post Mortem Examination: The pathologist's hand is grasping the large, hard tumor behind the stomach.

versely towards the pyloric end of the stomach. If the table were to be lowered to a horizontal position, with the patient lying prone upon it, the combined forces of the pancreatic tumor, the abdominal aorta, and the curve of the spinal column would then exert so much pressure upon the stomach as to cause its anterior and posterior walls to touch, thereby entirely expressing the opaque meal from its middle and no longer showing the extent of the retrogastric mass. Roentgenologically, this is as undesirable as is the appearance of the fully filled stomach when the patient is examined standing in the vertical position.

That the tumor mass producing the pressure is really extra-gastric and not a lesion of the mucosa of the stomach itself is proven by the presence of uninterrupted lines in the gastric mucosal pattern. This, too, can be revealed by the same procedure of tilting the table to the angle where, under direct roentgenoscopic control, there is obtained the desired amount of stomach compression necessary to bring out these gastric rugae. The neoplasm of the body of the pancreas will now act as the compression device for demonstrating the gastric mucosal topography.

DISCUSSION

Malignant neoplasm in the body and tail of the pancreas, but not involving the head of this organ, is really not rare. In a series of fifty proven cases of primary carcinoma of this gland, reported by Heck and Mortimer (6), this location of the growth was found nearly as often as was carcinoma of the head of the pancreas. But the clinical recognition of carcinoma of the body or of the tail of the pancreas is infrequent. Here the neoplasm does not encroach upon the extrahepatic biliary ducts and does not produce the obvious symptom of progressive, painless jaundice, such as it frequently does when involving the head of the pancreas.

In a recent issue of this Journal, Vorhaus (3) relates that, after reviewing the literature on the subject, he "could not find a single report of the clinical and roentgenologic findings which would enable such a diagnosis to be established." The case, which he correctly diagnosed as one of carcinoma of the body of the pancreas, he therefore believes to be the first of its kind to be reported. If that be so, then the one described here as a practical application of the recommended roentgenologic maneuver is the second reported case of carcinoma of the body and tail of the pancreas to be recognized by its clinical and roentgen pictures.



Fig. 4. The several small and one large area of metastatic carcinoma are seen on the under surface of the liver.



Fig. 5. The cut surface of the liver shows numerous islands of metastatic carcinoma.

CASE REPORT

The significant points in the history of this sixty-five year old white man were severe, sharp pain in the epigastrium, radiating to the left hypochondrium; his preference for sleeping in a sitting posture, or, even better, while leaning forward with his head and shoulders resting on a table, because, in this position, he had the least abdominal pain; the progressive loss of weight and strength; and the roentgenologic findings of a tumor mass behind the stomach.

He came to the office two weeks after the onset of pain in the upper abdomen, and related that food and alkaline powders made his symptoms worse. The pain was sharp and burning in character, and would radiate to the left hypochondrium. He had discovered that lying on his back accentuated the pain, and that sitting up or leaning forward diminished it. Hence, he elected the latter position for comfort. He would prepare for a night's sleep by pulling an easy chair against a table. Then he would place a pillow on the table, lean forward, and rest his head upon it. In this posture, he could find relief of the abdominal pain. There were no other important symptoms. There was no nausea nor vomiting, and there was nothing un-

usual in the character of his stools. He had lost fifteen pounds in the previous several weeks.

With this weight loss, the abdomen lent itself to satisfactory palpation. Nevertheless, no pathological masses could be felt at this time. The smooth liver edge was just below the right costal margin. Tenderness on moderate pressure was elicited in the epigastrium. Nothing unusual was observed or heard in the abdomen. There were no palpably enlarged lymph nodes in the groins, axillae, neck, or supraclavicular regions. The remainder of the physical examination brought to light no findings of pathological significance pertinent to this case report.

Of the laboratory studies performed at the office, the roentgenologic findings were of the greatest aid in arriving at the correct diagnosis. The X-ray revealed an area of diminished density in the mid-portion of the barium-filled stomach, which corresponded in location to the region of epigastric tenderness noted on physical examination. Yet no tumor mass could be palpated, even under direct fluoroscopic control. Moreover, this filling defect of the stomach was not due to any intrinsic gastric lesion, since there was no distortion of the gastric mucous rugae. Neither did the defect move along with the stomach when the latter was manually displaced. With the patient standing erect, the stomach shadow appeared evenly dense throughout. But as the tilt-table was inclined, a slight negative filling defect appeared along the lesser curvature of the stomach, above its *incisura angularis* (Figure 1). As the tilt-table was brought farther down, the defect extended over a greater area of the stomach, and pointed towards the pylorus (Figure 2). This roentgenologic finding was interpreted as due to a retrogastric tumor. Its anatomic location and extent led me to diagnose it as a tumor of the tail and body of the pancreas, clinically malignant.

The patient's condition became progressively worse. He developed more pain; he lost more weight; and he became weaker. Three weeks after the office examination just described, he was admitted to the Montefiore Hospital on the service of Dr. L. Wechsler. There he remained until his death, sixteen days later. At about the time of his admission, the tumor mass noted roentgenologically had so increased in size that it became palpable in the upper abdomen. The size of the liver had progressively increased also, and its edge was now distinctly nodular. He never showed any obstructive involvement of the biliary tract. He did not develop jaundice. Two weeks before his death, the icteric index was only plus three, and the bromsulphothalein test for liver excretion showed only 10% of the dye retained in the circulation one hour after its injection. His urine was always free of sugar. The blood sugar was 108 mgm. per 100 c.c., the N.P.N. 32, and the creatinine 1.3. Only shortly before his death did the N.P.N value rise to 50 mgm. per 100 c.c. of blood.

Permission for *postmortem examination* was limited to the abdomen only. The autopsy was performed by Dr. Yardumian, pathologist to the Montefiore Hospital. The following is a summary of his detailed report:

1. Adenocarcinoma of the tail of the pancreas with advanced degenerative changes and fibrosis.
2. Infiltration of the body of the pancreas by the same neoplasm. The head of the pancreas was not involved.
3. Metastatic adenocarcinoma of the liver with chronic hepatitis.

DISCUSSION OF FINDINGS

In addition to considering the roentgenologic technique which aided considerably in arriving at the correct diagnosis in this case, it would be well to summarize the other laboratory tests, and also the clinical symptoms and physical findings which contribute to the recognition of carcinoma of the pancreas, particularly of its tail and body.

First is the history of pain in the epigastrium, aggravated by the ingestion of a meal. Engel and Lysholm (7) refer to this as the "pancreatico-solar syndrome." They explain that this symptom of pain is due to irritation of the coeliac nerve plexus by the tumor of the tail and body of the pancreas. The weight of the food-filled stomach pressing against the coeliac plexus also increases its irritation and so elicits pain. Similarly, lying supine, or even leaning backwards, produces pressure against it. This leads to deep-seated epigastric pain, which may extend to the back and radiate as along the course of an intercostal nerve. It may simulate the segmentary pain of radiculitis. Heck and Mortimer (6) also mention the frequency of pain radiating to the back when the lesion is in the body of the pancreas. Recently, another illustrative case of such "pancreatico-solar syndrome" was described in "Case Records of the Massachusetts General Hospital" (8), in which the diagnosis of carcinoma of the body of the pancreas was determined at necropsy.

The physical findings are not typical. Eusterman and Wilbur (9) comment on the high incidence of palpable tumors in their series of eighty-eight cases. Yet the frequent mobility and variation in position of such tumors contribute to the difficulty of preoperative diagnosis. In the cases of neoplastic involvement of the head of the pancreas, this variability in the location of the tumor mass is most pronounced. In the instance reported by Hess (10), the tumor mass was in the right lower abdomen and freely moveable. On the other hand, no tumor may be palpable until relatively late in the course of the disease, as illustrated by the case reported here.

In the light of these rather inadequate subjective and objective signs, it is natural that one should turn to the laboratory for some aid. Such laboratory studies are directed to the investigation of this gland's function, and to the demonstration of a tumor in its form. The known functions of the pancreas are the liberation of its endogenous insulin, and the secretion of its exogenous digestive enzymes. Although the clinical deficiency of the former is readily recognized by the resulting hyperglycemia and glycosuria, yet such an occurrence seldom exists in carcinoma of the pancreas. As a rule, the neoplasm does not involve the Islands of Langerhans, at least, not until the destruction of the gland has become far advanced. The analysis of duodenal contents for the qualitative and quantitative determination of pancreatic enzymes seems a reasonable investigation, but in actual practice "the experience of most observers has been that the technical details of such methods (of examination) are too complicated and the information too meager and unsatisfactory to warrant their routine employment" (11). The recent studies on serum lipase reported by Comfort (12) showed positive findings in but fifteen out of forty-five instances of carcinoma of the pancreas. Hence, this examination, too, can be considered of contributory value in only about one-third of the cases.

The remaining laboratory procedure is the search for tumor changes in the form of the pancreas. This is accomplished by the roentgen studies already described in the preceding paragraphs.

CONCLUSIONS

1. The roentgenologic examination is a valuable laboratory aid in recognizing a tumor in the body or tail of the pancreas.
2. The indirect signs of such a tumor of the pancreas are the expansion of the horse-shoe curve of the

duodenum, obstruction of the duodenum, or a filling defect of the stomach produced by pressure of the extrinsic mass. Such a gastric filling defect need not be constant. Sometimes the tumor may not be large enough to produce much distortion of the stomach. Evidence of this retrogastric mass can then be elicited only when aimed pressure is applied to the anterior abdominal wall. To obtain such pressure, a roentgenologic technique is described here.

The patient, after ingesting the customary barium meal, is placed erect against the vertically tilted X-ray table, his abdomen against the table top. Under direct fluoroscopic control, the table is gradually lowered until a point is reached where the stomach is pressed upon by the structures lying behind it. These include the spine, the abdominal aorta, and body of the pancreas. When there is present a retrogastric tumor, such as carcinoma of the body or tail of the pancreas, the filling defect of the stomach becomes noticeable soon after the table has begun to be inclined. It again disappears when the patient is replaced in the vertical position. One must also observe the normal gastric rugae in this region which indicate that the tumor does not involve the stomach itself.

3. The value of this procedure is illustrated by the presentation of a case where its application made possible the correct diagnosis of carcinoma of the tail and body of the pancreas.

4. This case seems pertinent for discussion here because: (a). This location of the lesion is relatively not infrequent; (b). Any such laboratory aid as the roentgenologic technique suggested above should be welcome, since the recognition of carcinoma of the body of the pancreas is seldom accomplished prior to exploratory laparotomy or necropsy; (c). This is believed to be the second case reported where the clinical diagnosis of carcinoma of the tail and body of the pancreas was established on the basis of its clinical and roentgenologic signs.

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SECTION V—*Therapeutics*

The Etiology and Therapy of Ulcerative Colitis*

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IT is not generally realized that ulcerative colitis is now a very common disease. We see approximately 125 cases yearly at Mt. Sinai Hospital. Typhoid fever, formerly so prevalent, is now a rarity. The cause of this apparent increase in the incidence of colitis is conjectural: (1) if it is related to the tropical diseases, the marked increase in amoebic and bacillary dysentery in this climate may explain it. (2) if it is primarily a functional disease, in the sense that neurogenic influences may render the colonic mucosa more susceptible to infection, one should point out that all of the functional or so-called "diseases of civilization" seem on the increase at present.

Certain features of the clinical course are worthy of emphasis. This disease, with its bloody and purulent diarrhea (rarely constipation), running a febrile (or afebrile) course, is essentially a chronic illness. It is characterized, like peptic ulcer, by spontaneous exacerbations and remissions. Recurrences are the rule. It is doubtful if a severe case of ulcerative colitis, belonging to the group with an undetermined etiology, ever recovers and remains well throughout life. It is indeed a serious malady. Some years ago, in a survey of a 10 year period at Mt. Sinai Hospital, I found that the medical mortality was 18% in the severe, hospitalized group.

Under the term "ulcerative colitis" are included three groups of patients: (1) those with amoebic colitis. (2) those with bacillary dysentery, and (3) ulcerative colitis of undetermined etiology. The differentiation of the indeterminate group from amoebic and bacillary dysentery is usually an impossible task at the bedside or by means of the sigmoidoscopic or radiographic evidence. It is a laboratory problem—often a very difficult and at times an impossible one to solve. Before entering into a further discussion of the etiology, a few interesting pathologic and radiographic features should be mentioned: (1) secondary

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polyposis is quite frequent (13%). (2) perforation occurs in 3% of the cases. Such perforations are often very insidious and always fatal. (3) the sigmoidoscopic, pathologic, and radiographic findings frequently do not correspond with the clinical state. (4) it seems probable, but by no means proved, that the following forms of colitis; viz., diffuse ulcerative colitis, localized ulcerative colitis, ulcerative ileocolitis, regional ileitis, and granulomatous localized or diffuse ulcerative colitis or ileocolitis, are all varied expressions of the same fundamental disease process. We have seen, not infrequently, the transition from one of these types to the other in the same case. This is particularly true of that type of diffuse ulcerative colitis which eventually leaves as a residue, a localized granulomatous lesion in the ileo-cecal region.

While it seems that all these diseases form one group, one type may be split off which probably is a separate entity, viz., regional ileitis of unknown etiology. This lesion, found by Dr. A. A. Berg in his operative material and described by Doctors Crohn, Ginzburg and Oppenheimer, is an inflammatory lesion involving usually the last 8 or 10 inches of the ileum, usually terminating abruptly at the ileocecal valve—with some proximal so-called "skip" areas—with mucosal ulcerations and marked mural thickening (chiefly submucosal fibrosis)—with inflamed lymph nodes—and with fistulae and stenoses. Clinically, it simulates ileo-cecal tuberculosis, cecal neoplasms, acute and chronic appendicitis, ulcerative ileo-colitis, chronic abscesses with fistula formation, and various degrees of intestinal obstruction. It can be diagnosed by the clinical picture plus careful radiographic studies of the small intestine. It is not a very rare disease—we have collected approximately 60 cases in Mt. Sinai Hospital in recent years. The diagnosis of this disease is of great importance since the complete excision of the affected part seems to cure the patient.

In discussing the difficult subject of the etiology of these ulcerative diseases of the terminal ileum and colon, it seems desirable in the present state of knowledge, to be very conservative and careful in the expression of one's opinions. While ulcerative colitis is a fairly definite clinical and pathologic disease picture, it is doubtful if it is an etiologic entity. It is chiefly because of certain technical difficulties in the laboratory that there exists so much confusion in the discussions of its etiology.

Our personal experience is that a small per cent of typical chronic ulcerative colitis cases are instances of amoebic colitis. Often it is extremely difficult to find the organism. Also, at times, the therapeutic test with emetine and carbarsone fails. Recently, using the urinary bladder punch through the sigmoidoscope we have found amoebae in the biopsied tissues in a few cases in which repeated stool examinations were negative. Another group, perhaps 20 per cent, which seem to be of unknown etiology are really specific, viz., bacillary dysentery. In discussing the relation of the bacillary dysentery group to the remainder, that is, those with an indeterminate etiology (the other 75 per cent), we encounter many difficulties. It should be admitted at once that the chronic bacillary dysentery resulting from acute epidemic bacillary dysentery may be indistinguishable from the ulcerative colitis sporadically encountered. Although, after epidemics of bacillary dysentery some 2½ to 5% become chronic ulcerative colitis cases (often without any evidence of bacillary dysentery except the historical), nevertheless, it does not seem correct to assume that all, or even a large per cent of the ulcerative colitis cases of unknown etiology, are chronic bacillary dysentery. Even if one would like to feel that non-specific ulcerative colitis and chronic bacillary dysentery are one and the same, the evidence, as we shall shortly point out, is lacking for the establishment of this point of view.

For several years, under the direction of Gregory Shwartzman, Hershberger and Winkelstein (1) have been studying the relationship of indeterminate ulcerative colitis to bacillary dysentery. We studied a consecutive series of cases of sporadic ulcerative colitis patients in the wards of the hospital, chiefly in the years 1929 to 1933, for dysentery organisms, for dysentery agglutinins in the blood, and for dysentery bacteriophage in the stool. We found that 7 cases (11%) of typical "non-specific" ulcerative colitis had the organisms of bacillary dysentery in the stools; that approximately 20% had agglutinins for dysentery organisms in a titre above the normal expectancy (the normal expectancy of agglutinins for the Flexner strain is 1:100, for the Shiga, 1:50, and for the Sonne-Duval, 1:20) in the blood; and that 15 or 36% of 41 consecutive cases had a bacteriophage in the stool specific for one or another strain of the dysentery organisms. Forty-five consecutive controls, including several miscellaneous diarrheas, did not reveal an anti-dysentery bacteriophage in their stools. We concluded, with considerable caution, that this is suggestive evidence of a possible relationship in some of the cases of ulcerative colitis to bacillary dysentery. It is now necessary to explain why we were so careful in our conclusion about this relationship. We will first point out the difficulties in concluding from the laboratory data about the agglutinins, bacteriophage and even the organism, that chronic ulcerative colitis is acute or chronic bacillary dysentery.

Agglutinins for dysentery organisms, while usually not of a very high titre, may occur in the blood of normal people. Often exercise, a fever, or an unrelated disease (for example, typhoid fever), may bring out dysentery agglutinins. The mere finding of agglutinins in the blood is not diagnostic of bacillary dysentery. Cross agglutinins from closely related bacteria (B. Coli) may also confuse the situation. Agglutinins may appear and disappear rapidly, or, may appear late, or, may not appear.

While it is true that a bacteriophage for dysentery organisms may appear in the stool in patients as they are recovering from bacillary dysentery, this is not necessarily associated with the dysentery organism. A bacteriophage adapted to a Gram-negative organism in the gastro-intestinal tract may readily become adapted to several other organisms of the same group.

In practically every stool there may be a weak bacteriophage for the B. Coli. This bacteriophage may, at times, become strongly lytic, not only for the harbored B. Coli, but also for closely related stock dysentery organisms. The mere finding, then, of a dysentery bacteriophage in the stools of a patient with ulcerative colitis does not prove that the patient has or has had an infection due to the organisms of bacil-

lary dysentery. It may possibly signify such a state, or, it may signify a different or changed strain of B. Coli. Our statistical evidence, i. e. the finding of a dysentery bacteriophage in a fairly high percentage of the cases of ulcerative colitis of undetermined etiology and not in normal and miscellaneous controls, is, however, somewhat suggestive of the dysentery origin of the disease but,for the reasons just cited, not conclusive evidence.

Finally, the strongest evidence comes up for discussion, viz., the finding of dysentery organisms in the stools. The identification of the organisms requires great care. The cultural characteristics alone are insufficient. In fact, using the cultural characteristics alone for diagnosis, one would be forced almost each day to report atypical B. Coli obtained from various sources (gall bladder, genito-urinary tract, normal stools) as dysentery organisms. The agglutination in high titre of the organism by specific sera is absolutely essential for the diagnosis of an organism as a bacillary dysentery strain. Not only do these considerations from the laboratory offer obstacles but there are other serious objections to the idea that chronic bacillary dysentery and ulcerative colitis are identical. Ulcerative colitis is usually sporadic; bacillary dysentery is usually epidemic. Ulcerative colitis is almost never encountered as a contact disease; nor do certain geographical localities furnish more cases than others. Ulcerative colitis usually begins insidiously; bacillary dysentery is as a rule acute and stormy in its onset. Dysentery attacks all ages, particularly children, while ulcerative colitis usually hits young adults. As already pointed out, the pathologic, sigmoidoscopic, stool, and radiographic features of any chronic ulcerative colitis (amoebic, bacillary, or, indeterminate) may be identical although the etiology differs. This, of course, is probably due to the importance of the secondary invaders in the chronic stages of these diseases.

Our opinion in the matter of the etiology of chronic ulcerative colitis may be summarized as follows: (1) a small per cent are unrecognized amoebic colitis cases. (2) a certain per cent, approximately 20%, are instances of chronic bacillary dysentery in whom either the dysentery organisms or the secondary invaders, or both, keep up the disease. (3) the cause in the remainder is as yet unknown. What Bargen has described is probably a group of secondary streptococcic invaders. Three theories seem most plausible: (1) a primary functional (neurogenic) disturbance of the bowel and then a secondary infection. (2) the mucosa is first sensitized by a transient specific or special infection and then local or distant organisms or toxins attack the susceptible tissues (Shwartzman). (3) the specific cause, whether bacterial or virus in nature, is yet to be discovered.

We may now leave this discussion of the etiology and take up some of the therapeutic measures in the group of patients with ulcerative colitis of undetermined etiology. It is necessary to emphasize that we do not know the etiology in this group. Therefore, an ideal therapy, based on the cause and mechanism involved, cannot be realized. In the light of our present knowledge, we are forced to conclude that it is not an etiologic entity and we must base our therapy on the most rational concepts. These we have already outlined.

Some of the fundamental principles of therapy which should be kept in mind are: (1) this is a chronic disease with sudden spontaneous remissions and exacerbations. Great care, therefore, must be exercised in the interpretation of therapeutic results. (2) in view of the close relationship of the vegetative nervous system to the alimentary canal, all sorts of factors, particularly psychic and reflex, may play an important role. (3) in presenting therapeutic studies a sharp definition and clear differentiation of the group of patients under treatment should be stated. Obviously, it is a matter of great importance as to whether we are treating mild, moderate, or severe cases of ulcerative colitis. The mild cases perhaps require only rest, fresh air, sunshine and a good diet, i.e. hygienic therapy. In this discussion we are considering the more severe cases or so-called "colitis gravis,"—the in-bed, hospitalized group with fever, with bloody and purulent diarrhea, with severe ulceration, with advanced radiographic changes, with emaciation, anemia, and toxicity. (4) therapeutic results which are not interpreted and presented in the light of a complete study, viz., clinical, sigmoidoscopic, stool, and radiographic features, are not worthy of attention. (5) to claim the value of any single therapeutic measure, it must be used in a large group of cases of the same type and a striking, sudden, dramatic improvement must take place, within a few days to two weeks, in most of the cases so treated. Otherwise the improvement may be merely coincidental. (6) individualization in the treatment, good nursing, therapeutic resourcefulness, excellent clinical judgment, and, fine psychotherapy are highly desirable in the treatment of this disease.

Having stated most of the fundamental principles we may now consider separately the various therapeutic measures:

I. *Rest in bed.* This must be for a long period. Patients and their families must be warned of the prolonged, chronic nature of the malady. Occasionally, in the milder, chronic cases a change from bed to the open air and sunshine will produce a remarkable and rapid improvement.

II. *Diet.* The diet which I have instituted on the wards of Mt. Sinai Hospital in the treatment of ulcerative colitis is given here.

DIET FOR ULCERATIVE COLITIS USED IN THE MOUNT SINAI HOSPITAL, NEW YORK CITY

Breakfast:

Orange juice or grapefruit juice
Stewed fruit (strained)
Eggs—soft or hard boiled or poached
White bread or toast with butter or jelly
Buttermilk, thin cocoa, or tea.

Noon Meal:

Small portion scraped beef or lamb, lamb chop, fish, minced white meat of chicken (not fried)
Boiled, mashed, or baked potato
Strained asparagus, carrots, string beans, spinach, tomatoes, peas
Stewed fruit (strained), as pears, peaches, applesauce, ripe banana, custard, junket, jello
White bread or toast with butter or jelly
Buttermilk, thin cocoa, or tea
Tomato juice.

Supper:

Milk soup with strained vegetables, or clear soup
Eggs—soft or hard boiled, or poached
Small portion cream or pot cheese
Well-cooked cereal with milk and sugar or strained vegetable as above
Stewed fruit (strained), ripe banana, custard, junket, or jello
White bread or toast and butter
Buttermilk, thin cocoa, or tea.

It is well-balanced in protein, fat, and, carbohydrate. Milk is usually not well tolerated. Some observers have claimed that there is a primary or secondary avitaminosis, or, a "deficiency" state in the disease. While the evidence for this is not strong, it seems theoretically desirable to give Haliver Oil, Viosterol, yeast, cevitamic acid, ultraviolet rays and calcium. We have not seen any striking results from vitamin-rich foods or the administration of these substances, yet we continue to use them.

III. *Diarrhea.* The bowel movements are actually sanguino-purulent discharges rather than diarrheal stools. Hence the fallacy of most of the therapeutic measures which are directed against true diarrheas. Opium is the best drug, particularly when given at night to insure rest. Atropine, kaolin, and bismuth usually do not help very much. I have recently received from Dr. A. Koenig, of the Mellon Institute of Industrial Research, a vegetable gum rich in bassorin, which, taken in the form of a mucilage (a teaspoonful in a glass of water t.i.d.) by mouth, seems to increase the consistency of the stools, and, in some instances, clinical improvement. Substances like carob gum used similarly also help but apparently to a lesser degree. Often cleansing enemas (normal saline or 1% bicarbonate of soda), heat to the abdomen, and rectal installations of warm olive oil (with or without a teaspoonful of bismuth subcarbonate or subgallate) seem of value in the control of rectal discharges, tenesmus, or, discomfort.

IV. *Colonic Treatments.* A. *General.* The use of colonic irrigations, enemas, and rectal instillations is of doubtful value. They may spread infection. Some patients cannot tolerate them. Bicarbonate or saline enemas as stated may be cleansing and thus lessen the discharges. In chronic, sluggish ulcerative states, 1% tannic acid or silver nitrate (1:5000 or 1:2000) enemas may stimulate healing. Olive oil with bismuth subgallate as a rectal instillation may sooth an irritable rectum and sphincter.

B. *Antibacterial.* During the last 2 years we have had some interesting experiences with a new chlorine compound, "Azochloramid." This is an organic chloramine discovered by Schmelkes and collaborators (2, 3, 4), accepted by the Council on Pharmacy & Chemistry (5, 6). It is distinguished from other chlorine compounds by the slow rate with which the chlorine is liberated, permitting the preparation of stable solutions which retain active chlorine for considerable periods of time, even in the presence of such organic matter as pus or fecal matter. The chlorine is liberated from this compound so slowly that its solutions are odorless and a solution of azochloramid in olive oil (1:2000) such as I have utilized in my clinical work is applicable to the colonic mucous membrane without causing undue irritation. Due to the variety of the bacterial flora in the human intestine, antiseptic treatment would seem to have the best chance of success if a substance of non-selective bactericidal properties is used. Laboratory findings suggest that azochloramid should have such an effect.

I have therefore used azochloramid in olive oil (1:2000) as a rectal retention instillation (III to VI b.i.d.) in 25 cases of indeterminate ulcerative colitis. In somewhat more than half of these cases good results were seen. Within ten days there was subjective and objective improvement. Irritation was rarely encountered. In one case, acutely and severely ill for 1 year, where all other measures had failed, a brilliant result was obtained in 2 weeks with the use of this preparation. It seems worthy of careful clinical trial.

V. *Transfusions.* The use of fairly large (500 c.c.) repeated blood transfusions is perhaps the single most important therapeutic measure in this disease. Following a transfusion, one witnesses occasionally, a sudden, dramatic improvement, almost in the nature of a crisis. How such a result is brought about is only conjectural. Certain human sera may be strongly antitoxic to whatever toxins or viruses are responsible for the illness.

VI. *Specific measures.* Insofar as the etiology of the disease is not definitely established, the seeming multiplicity of specific etiologic factors makes the use of more or less specific measures desirable. The specific measures may be discussed under the following headings: (a) anti-amoebic; (b) anti-dysentery; (c) Bargen's serum; (d) vaccine therapy; (e) antitoxic B. Coli horse serum; (f) bacteriophages; (g) foreign protein shock.

(a) *Antiamoebic therapy.* Even if the organism is not found, we, nevertheless, institute a course of antiamoebic therapy. We feel that emetine hydrochloride, grs. 1 intramuscularly, daily for 10 days, together with carbarsone (0.25 gm. b.i.d for 10 days) is a good therapeutic test. Anayodin often causes an increase in abdominal discomfort and diarrhea and its use does not seem indicated as a therapeutic test. (In proved amoebic colitis, it seems very valuable). It must be admitted that we have rarely seen a striking result in the cases of undetermined etiology with this form of treatment.

(b) *Anti-dysentery measures.* When there is evidence at hand indicating strongly that the case is probably one of bacillary dysentery (i.e., the finding of the organism, a very high agglutinin titre, together with a potent anti-dysentery bacteriophage), polyvalent anti-dysentery serum should be used. It is necessary to have a serum which is strongly antitoxic and to administer it in very large doses within a short period of time. We have treated some cases in this fashion (giving within 3 days 350-400 c.c. of serum intravenously in divided diluted doses by the drip method) and we have seen some brilliant results. We have not been impressed with the results of the rectal instillations of anti-dysentery bacteriophage. Dysentery vaccine and toxin for immunization have not been tried.

(c) *Bargen's serum.* It is quite probable that some of the streptococcus strains play a rôle as secondary invaders. In view of our experience that large doses of serum seem desirable, it is possible that the use of Bargen's serum in very large doses intravenously might conceivably give better results than we have seen in a moderately small series of cases treated with

small doses of Bargen's serum subcutaneously and intramuscularly.

(d) *Antitoxic B. Coli horse serum.* On finding that the B. Coli has a powerful, soluble exotoxin, Gregory Shwartzman prepared an antitoxic horse serum using pooled strains of B. Coli and B. Coli toxins. This serum was strongly antitoxic as measured by the Shwartzman phenomenon (35 to 75 "phenomenon neutralizing" units per c.c.). As mentioned above, the experimental evidence provided by the Shwartzman phenomenon points to a possible concerted pathogenic effect of unrelated micro-organisms or their soluble toxic products. On the basis of this evidence, the idea occurred to me that the colon bacillus may be a very important primary or secondary invader in ulcerative colitis and therefore we instituted the antitoxic B. Coli horse serum therapy of nonspecific ulcerative colitis. (This therapy has been reported (7) elsewhere but a brief resumé will be given here). In the last year and a half 35 cases have been treated with this serum.** Only severe cases with toxicity, fever, bloody and purulent diarrhea and severely ulcerated bowels were selected for this therapy. If careful sensitization tests (conjunctival and intradermal) were negative, the serum (350-400 c.c.) was given, diluted in saline, in divided doses, using the slow intravenous drip method, spread over 2½ to 3 days. Preceding each intravenous injection, adrenalin was given. Immediate shock, chills, or sharp temperature rises were not encountered. Serum sickness occurred 5 to 10 days later. In 28 cases the results were strikingly good. In a few days to 2 weeks the temperature became normal, the stools were reduced to 1 or 2 formed movements, the mucosa healed, and the patient gained weight. In 3 cases, the patients improved after several weeks. In 4 cases, there was no improvement. Considering the type of case treated, these results are very encouraging. No conclusions should be drawn from this about the relation of the colon bacillus to ulcerative colitis. Intensive studies are being carried on now in our laboratory by Shwartzman, Hirshberger and myself, on the colon bacillus, its toxin, the preparation of new sera, the preparation of concentrated sera, and the possible specificity of certain strains of B. Coli found in ulcerative colitis. Immunologic studies with B. Coli toxin and antitoxin in animals and humans, in ulcerative colitis and other diseases, are also in active progress.

(e) *Vaccine therapy.* Our experience with Bargen's vaccine and vaccine filtrate is too limited to permit of presentation. The results of autogenous vaccines which were given routinely in a large number of the chronic cases, are difficult to evaluate. From our previous discussion of the rôle of the colon bacillus, it is obvious that it may be possible soon with further immunologic studies to quantitatively estimate and increase the B. Coli antitoxin in patients using B. Coli vaccine and B. Coli toxin. This is now being attempted on our colitis patients using skin tests and the Shwartzman phenomenon in the estimate of the antitoxic effects.

(f) *Bacteriophage.* While the results of the rectal instillation of anti-dysentery bacteriophage have been disappointing, it is possible that B. Coli bacteriophage (perhaps against certain specific strains found in ulcerative colitis patients) may prove more helpful.

**The antitoxic B. Coli serum work was made possible by a grant from The Friedsam Foundation which is gratefully acknowledged.

(g) *Foreign Protein Shock.* The explanation of our success with serum therapy (either anti-dysentery or anti-B. Coli) is probably not foreign protein shock, since, as already stated, we did not produce shock in our cases. We have utilized in a few cases intravenous typhoid vaccine to evoke chills and fever, without beneficial results. We are now undertaking a study of the effect of artificial hyperpyrexia on this disease.

(h) *Surgical therapy.* Surgical therapy for ulcerative colitis is indicated only under certain conditions. The indications are, briefly, four:

(1) for perforation, obviously.

(2) for localized, hypertrophic lesions which, wherever possible, should be completely removed, preferably with a preliminary anastomosis (ileo-colostomy).

(3) In the acute, septic, fulminating cases with a rapid downhill course, ileostomy may prove a life-saving measure. The type of case and the time of the institution of this form of surgical therapy requires rare clinical judgment.

(4) Where severe complications exist in the chronic, intractable cases such as strictures, polyposis, perirectal sinuses and suppuration, peri-sigmoid suppuration or massive hemorrhages, ileostomy should be instituted.

Appendicostomy, cecostomy, ileosigmoidostomy, partial or complete colectomy may be mentioned only to be condemned. The results are poor and the risks too great.

There are also strong objections to ileostomy. It is difficult to decide when to operate. The immediate mortality is high and the late mortality is considerable. It does not cure the disease. Even septic attacks occur in the presence of the ileostomy. In most instances, it must be permanent, for, if removed, the colitis recurs in a very severe form. A few years ago I sent a questionnaire to the leading surgeons and gastro-enterologists of the United States concerning ileostomy. The answers to the questionnaire giving information about 186 cases with ileostomy for ulcerative colitis bear out the impressions herein stated. In those cases—not an inconsiderable number—where the lesion is chiefly in the proximal colon (and terminal ileum) and where the rectum and sigmoid are normal or nearly so, Dr. A. A. Berg has suggested and used low ileosigmoidostomy with transection of the sigmoid closing the distal end and leading the proximal cut end of the sigmoid externally as a sigmoid colostomy. This procedure may prove valuable as such or as a preliminary operation to a later partial colectomy.

SUMMARY AND CONCLUSIONS

Ulcerative colitis is now a common disease, characterized by a chronic, recurrent course. Its clinical and pathologic features do not distinguish it from the specific colitides. Etiologically, it does not seem to be an entity. A few cases are unrecognized amoebic colitis. A larger percentage (perhaps 20%) are chronic bacillary dysentery. The etiology in the remaining majority is unknown. It may be that the ileocolic tissues rendered susceptible or vulnerable by a previous specific infection may be attacked recurrently by local or distant bacteria or their soluble toxic products, or, that the specific causative agent has not as yet been discovered.

In discussing the therapy in the indeterminate group the occurrence of spontaneous remissions should

always be borne in mind. In considering the conclusions presented about specific measures, the exact degree and the nature of the illness in the cases under treatment should be stated. The most valuable therapeutic measures seem to be: (1) Prolonged bed rest. (2) a full diet rich in vitamins and minerals. (3) opium and gums for the diarrhea. (4) saline, tannic acid, and silver nitrate enemas. (5) olive oil and Azochloramid rectal instillations. (6) repeated blood transfusions. (7) routine anti-amoebic therapy (emetine and carbarsone). (8) in proved cases of bacillary dysentery, massive doses of anti-dysentery serum. (9) in the cases of unknown etiology, antitoxic B. Coli horse serum (good results are herein reported with this form of therapy). (10) in the chronic, recurrent cases, active immunization with B. Coli vaccine and toxin in the interval stages. With reference to the surgical therapy, it may be stated that it is rarely indicated. In fulminating cases or in those with severe, chronic complications, ileostomy seems to be the best surgical procedure. For ileocolitis, where there is chiefly proximal colon involvement, ileosigmoidostomy with proximal sigmoid colostomy, preliminary to subsequent partial colectomy (Berg) seems to be a rational operative method worthy of trial.

In conclusion, we are impelled by our experience in recent years to revise our former pessimistic attitude concerning the prognosis in the severe cases of ulcerative colitis. Using the therapeutic measures herein described, there is apparently a decreased mortality and an improved clinical course in many cases.

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SECTION VII—*Surgery of the Lower Colon and Rectum*

The Variety and Distribution of Gross Lesions in Lymphopathia Venerea*

By

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IN the limited time assigned for this paper, it is obviously impossible to go into any large amount of detail. In selecting the title "Lymphopathia Venerea" I am using one which I consider more appropriate than "Lymphogranuloma Inguinale" which unfortunately has been so often confused with "Granuloma Inguinale," a skin disease, and with "Lymphogranulomatosis," which is another name for Hodgkins disease.

So much has appeared in literature in recent years that I must pass up any historical references, aside from the fact that in 1811 Thomas Copeland suspected the venereal origin of stricture of the rectum, and in 1859 Chassaignac spoke of a "peculiar inguinal node infection." In 1913 Nicholas, Durand and Favre recognized the condition as a pathologic entity and in 1922 Nicholas and Favre first used the name "Lymphogranuloma Inguinale" in place of the name "Nicholas-Favre disease." In 1925 Wilhelm Frei devised a specific skin test for this disease. In 1932 Wolfe and Sulzberger suggested the name "Lymphopathia Venerea" as being descriptive and avoiding much confusion in literature.

Lymphopathia venerea is probably a disease of great antiquity, and has been pretty well distributed over the world. One cause of confusion has been the difference in the manifestations in the male and female. In the male there is a primary penile sore, followed by a bubo, which may, or may not suppurate following the initial lesion. In the female the primary sore being situated in the vaginal wall or upon the cervix, is rarely if ever seen, while the predominating pathology is a stricture of the rectum. These differences have led us far astray in recognizing these two conditions as one and the same disease. In our experience 90% of the females are afflicted with rectal stricture, while only 10% involve the genitalia and inguinal glands. In the male these figures may be reversed, but in either sex both may exist simultaneously. The outstanding factor is also the marked difference in the expression of the disease in the white and the negro races. I am thoroughly in accord with Rosser, who in 1922 stressed the fibro-plastic diathesis in the negro race, showing that there was a marked tendency of all injured and infected tissue to develop thickening, pseudo-elephantiasis and keloidal degeneration or formation. Years ago I used the term "negromata" in describing this tendency to inflammatory tumor formation. In the white race we do have stricture formation, hypertrophies and pseudo or

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Submitted August 2, 1936.



Plate No. 1

real elephantiases, but these conditions are not so pronounced as in the negro race. Intermittent attacks of lymphedema with much less inflammatory reaction, seem to be more prevalent.

In any case and in either race, this disease runs a very irregular course, the symptoms and indurations subsiding to such an extent that cures have been reported, only to have the disease flare-up at varying intervals. I am extremely skeptical as to any permanent cure of this disease. Laboratory examination of the tissue frequently confuses us with reports of a chronic inflammation, lues, or tuberculosis. Two or three different reports may be made upon the same tissue by different laboratories, or upon the same patient in the same laboratory at different periods. Fortunately the Frei test will clear up the diagnosis, although lues, tuberculosis and other diseases may be associated. Particularly is this true in the colored race, which seems to enjoy acquiring a multiplicity of venereal infections.

As these cases are constantly visiting our clinics, persistently hospitalized, and everlastingly in a state of poverty, the cost to the community is an important, economic factor. As many of them work in restaurants and kitchens of private homes, certainly notice should be taken of the peril of spreading this infection. Our Philadelphia group of proctologists, assisted by



Plate No. 2

some of our urologists and dermatologists, has contacted about 360 cases in four and one-half years. Naturally in the proctologic clinic, the majority of the cases present the picture of rectal stricture. 90% of these are women, but after we interpret the studies made by Batson and Nesselrod upon the lymphatic circulation of the genito-ano-rectal area, we can see how it is possible that both sexes may be susceptible to all of the complications possible in this disease. I am endeavoring to call attention to the rather bizarre pathology. The various expressions of this disease may be noted as a bubo which may, or may not, look as if it had been operated upon, a urethral stricture, a rectal stricture, esthiomene and elephantiasis, multiple fistulae, recto-vaginal fistula or any combination of these.

We have come to the conclusion that when we encounter a condition in the genito-ano-rectal area that looks like nothing we have seen before, that looks like no other disease, that does not even look like itself, that we had better perform a Frei test to help clarify the diagnosis.

We know little of the life expectancy of the patients, as the Bureaus of Vital Statistics report the deaths

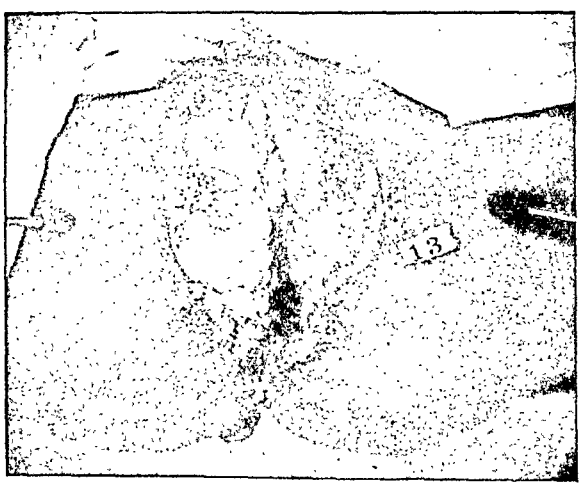


Plate No. 3

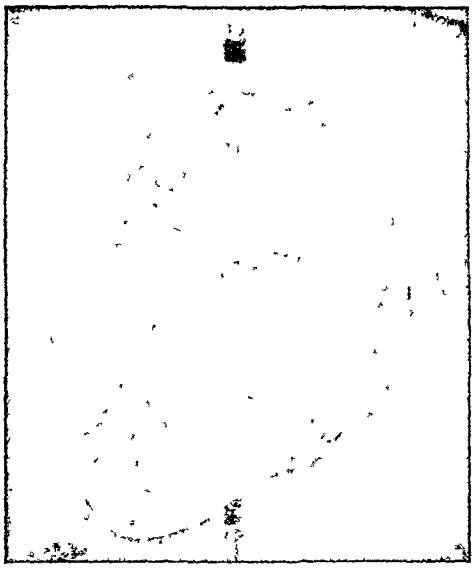


Plate No. 4

duc o everything except lymphopathia venerea. We do observe that, while we see many cases from 17 years of age and over, the number living after 50 years is comparatively small.

It would seem necessary to attend a few abbreviated histories with photographs, demonstrating the points stressed in this paper. Necessarily, much detail must be omitted.

Plate No. 1. G. W., female negress, aged 35, married twice; second marriage in 1926. Admitted to our clinic November 18, 1935. Present illness: difficult bowel movements. She says her constipation began in 1923. Operated upon that year in West Virginia for the obstruction. Operated again in Philadelphia in 1932; became progressively worse. Local examination showed elephantiasis of the vulva and esthiomene of the peri-anal tissues. Tubular rectal stricture of small calibre. Frei test plus 4, Wassermann negative. Husband examined gave Frei test plus 4. He reports a bilateral adenitis in 1927. Patient, G. W., admitted to Graduate Hospital, service of Dr. W. E. Lee, December, 1935, for preliminary colostomy. Patient decidedly anemic and rather bad cardiac condition with blood pressure 210/130. Had a preparatory blood transfusion, husband the donor, and intravenous glucose injection. Has dyspnoea on exertion and some edema of the ankles since 1929. *Operation January 6, 1936*, first stage of Lahey method for abdomeno-perineal dissection and double barrelled colostomy. Died January 15, 1936, with complicating uremia. Note: Tissue removed from perianal region and labia produced a very active antigen.

Plate No. 2. B. P., female negress, 23 years old, waitress. Massive elephantiasis of the labia, mostly on the left side, for the past two years. Frei test plus 4, Wassermann plus 4. Is being treated by the Dermantologic clinic for lues. Has been married for three years, but believes that her infection started at the early age of 13. Has beginning rectal stricture and also some inguinal scars on the left side, which she says began with an abscess five years ago. We hope to remove this tissue for purpose of producing antigens.

Plate No. 3. P. Y., female negress, 31 years old, single; service of Dr. Wm. H. Mackinney, Urology, Philadelphia General Hospital. Photographed April 30, 1936. First noticed ulceration four years ago; apparently healed after having some treatment by a private doctor. Tissue broke down again in November, 1935, and she was admitted to the Philadelphia General Hospital with a note that there was ulceration of both vulvae, and the condition was diagnosed as granuloma inguinale. Was given injections of tartar emetic and dismissed in January, 1936, apparently healed. Wassermann negative. We find on further search of history from the ward notes, that the patient had not entirely recovered, but was considered well enough for ambulant treatment. Readmitted March 23, 1936; wound broken down; ulceration involves entire recto-vaginal septum within one and a half inches of the cervix; also the perirectal tissues laterally and posteriorly. Tissue indurated. No rectal sphincter nor mucosa remain. Has incontinence and a rectal stricture of 8 or 9 caliber. She says her rectal bleeding began three and a half years ago. Clinically she has destruction of all perianal and perirectal tissue, as high as the level of the mid portion of the vagina. The ulceration includes the deep tissue of the entire perineum. She is very anemic; R.B.C. 2,310,000; hemoglobin 40%. Ulceration is so extensive that complete obstruction is not a clinical symptom. Frei test March 23, 1936, was positive subject to our's, later. Diagnosis was made of lymphopathia venerea. However, the Urologic service believes that in spite of the positive Frei test, the original diagnosis of granuloma inguinale is still valid. Note: Apparently no biopsy had been done and the chart shows no Donovan bodies have been at anytime demonstrated. Our query is, how could they be found without a biopsy? Frei test May 2, 1936, was positive with both

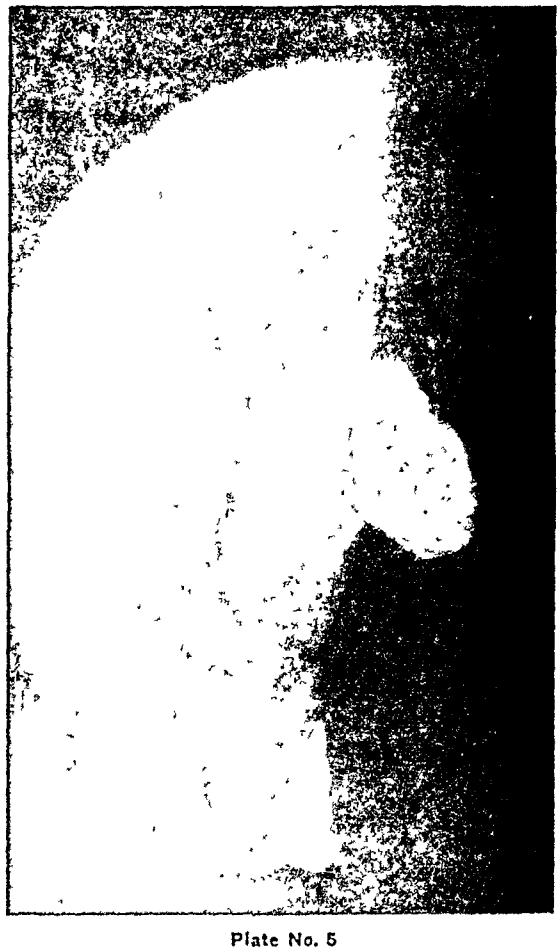


Plate No. 5

polyvalent antigen and antigen from G. W. Comment by Dr. Landreck, a student on our service: "We believe that she has lymphopathia venerea. If a biopsy is done and Donovan bodies can be demonstrated, we think that this is a case of double infection, namely lymphopathia venerea and granuloma inguinale."

Plate No. 4. W. J., colored male, 36 years old, single, lived in Philadelphia since birth. Admitted to Philadelphia General Hospital, service of Dr. Wm. H. Mackinney, three years ago, with granuloma inguinale, and apparently has received continuous treatment from that time. Has gained 137 pounds since admission. Lesion consists of bilateral adenitis, edema and elephantiasis of the penis, scrotum and perineum. *Apparently acquired infection in 1925.* While in the hospital condition healed and broke down several times. He reports that his inguinal glands were removed 15 years ago, which would bring the date of the primary infection to 1921. At the present time has edema and elephantiasis of the shaft of the penis and a general elephantiasis and fibrosis of the scrotum. Frei test is positive and we feel sure that this is a case of lymphopathia venerea and probably not granuloma inguinale as no Donovan bodies have been reported.

Plate No. 5. W. J., colored male, 40 years old, single, from Urologic Clinic, Philadelphia General Hospital, Dr. Wm. H. Mackinney. Case demonstrated as one of granuloma inguinale of the penis. Infection acquired in 1932 in Baton Rouge, La.; came to Philadelphia General Hospital fourteen months ago; diameter of shaft of penis at that time, four and one-half inches. Wassermann 4 plus. Frei test at that time, negative. Biopsy showed no Donovan bodies. Patient received injections of salvarsan and mixed treatment until Wassermann became negative. Some improvement after receiving tartar emetic injections and X-ray irradiation. Frei test positive April 11, 1936, and also April 13; antigens used polyvalent No. 2 and Vann. Reports from pathologic laboratory March 12, 1935, "acute phlegmanous cellulitis of penis" and April 9, 1936, "chronic hyperplastic lymphadenitis." In spite of the fact that no specific picture was shown upon examination of the tissue, we feel that this should not be expected in the chronic type of lesion; the acute bubo probably giving us the best picture. With the positive Frei reaction, the fibrosis and elephantiasis of the shaft of the penis, and elephantiasis and edema of the scrotum, would make us feel that this is surely a case of lymphopathia venerea.

SUMMARY

In summing up, we simply call attention to the immense variety of gross lesions encountered and the difficulty of diagnosis. The confusion between granuloma inguinale and lymphogranuloma inguinale, or lymphopathia venerea is possibly due to the fact that many of these cases of lymphopathia venerea do improve somewhat under injections of tartar emetic. That leaves us with only two points for a differential diagnosis: first, the presence of Donovan bodies in tissues removed, and second, the presence or absence of a reaction to the Frei antigen. We believe that the antigen is specific. We also believe the Donovan bodies to be diagnostic; therefore, should we find both, the patient must have two diseases.

SECTION IX—*Book Reviews*

(This section is open to contributions from any medical reader, whether or not a member of the Editorial Council).

MEDICAL Classics. Williams and Wilkins, Baltimore, Md., Vol. No. 1, September, 1936. Edited by Emerson C. Kelly, M.D., Albany Medical College, Medical Classics, while being published monthly, is not so much a journal as a series of small books, each more or less complete in itself. The first issue presents three of Sir James Paget's most important contributions to medicine, all printed exactly as written, with facsimile reproductions of the title pages of each article. Much biographical material concerning Paget is included. A preface states the nature of the publication and gives a forecast of subjects to be treated in early ensuing issues.

The format and printing are very attractive and live up to the traditions of the publishers. The material is extremely interesting to those who have a liking for historical fact. It is predicted by the reviewer that Medical Classics will meet with encouraging success.

Beaumont S. Cornell, Fort Wayne.

Physician, Pastor and Patient, by Geo. W. Jacoby, M. D., with an Introduction by Harlow Brooks, M.D. Published by Emerson Books, Inc., New York, June, 1936, 252 pages. Price $2.00.

THE author of this book, a past president of the American Neurological Association, has attempted to bridge the apparent gap between medical science and religion, and to establish a sound basis upon which the physician and the pastor may join their efforts for the betterment of the individual, not only as a patient but also as a member of the community. Hence he devotes several chapters to a somewhat brief, but for the purpose, satisfactory outline of the development of medical science and similarily, to the origins and development of the religious beliefs held by the various peoples of the world. Particular emphasis is laid on the changes that have occurred in personal hygiene and measures of health and type of medical practice in the centuries of progress which witnessed the breaking of the fetters of religious intolerance and led to the emancipation of the individual. Having thus established a common ground, the author discusses the major problems which confront both the physician and the pastor in his relation to the community. He is quite modern in his liberal attitude towards contraception, artificial abortion and birth control, and quotes freely from medical and religious sources, to maintain his point against the ironclad laws which obtain in Catholic regulations.

There are interesting chapters on the problems of suicide and insanity, divorce, criminality, sterilization, sex education, the mentally sick, euthanasia, vivisection and its role in the development of medicine and secrecy in medical ethics. Throughout he would

like to establish more friendly and cooperative relations between the physician and the pastor.

Although the book is somewhat choppy in spots, because of attempts to cover too much ground in the allotted space, it is fairly well written and should be of greater informative value to the layman than the physician.

Leon Bloch, Chicago.

Food, Fitness and Figure, by Dr. Jacob Buckstein.

THIS small but concise and well written volume comes at an opportune time. Much is being written about the question of weight reduction, mostly by individuals who have had no scientific training and whose advice is often not only worthless but actually harmful. In this very interesting volume Dr. Jacob Buckstein, a worthy authority, has incorporated not only worthwhile advice about foods and reducing diets but also diets for gaining weight. The entire subject of foods, vitamins, minerals, food values and the necessary amounts of food for healthy living is explained in scientific yet simple language for lay consumption.

There are many interesting chapters on the discovery and development of meats—vegetables—milk—fruits—nuts and beverages. Simple, yet convincing and scientific suggestions are made about such debatable subjects as coffee, tea, alcoholics, vegetarianism and fasting. The last one-third of the book consists of itemized diets for gaining and losing weight—food values—protein and vitamin contents of specific foods and specific amounts.

In short, here is a volume of information that can be recommended by a physician to his patient which not only needs no apology but which represents the best sound and scientific knowledge on the question of foods and weight reduction.

Y. N. Levinson, Chicago.

SECTION XII—"*The Clinic*"

Primary Leiomyosarcoma of the Upper Third of the Esophagus*

By

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and

RICHARD F. BIRGE, M.D.

PORTLAND, OREGON

THAT true leiomyosarcomas are rare is attested by the fact that Kraufkopf (1) in 1933 was able to find only thirty-one recorded cases in the literature. One of the least common sites of these tumors is the esophagus, and a case of leiomyosarcoma of the upper one-third of the esophagus, where the musculature is predominantly of the striate variety, has apparently never been recorded. Oddly enough, in two of the three reported cases of rhabdomyosarcoma of the esophagus, the new-growth occurred in the lower portion of the esophagus (Wolfensberger (2) and Glinski (3)). Dvorak (4) described the only case of rhabdomyosarcoma of the cervical portion of the esophagus.

The earliest case of primary leiomyocarsoma of the esophagus is that of Howard (5) who, in 1902, described the occurrence of a diffuse infiltrating mass in the distal twelve centimeters of the esophagus. There were associated ulceration of the esophageal mucosa and metastases to the stomach and regional lymph nodes. The new growth was a mixed cell sarcoma apparently divided wholly from the smooth muscle tissue of the esophagus, and Howard states that all graduations of cell types, from normal smooth muscle cells to the large tumor cells, could be traced. Von Hacker (6) reports Eppinger's case of leiomyosarcoma of the esophagus, stating that the tumor occurred as a polypoid mass filling the widely dilated lumen of the lower end of the esophagus. The tumor was composed of large, spindle-shaped cells with interspersing bands of white, homogeneous smooth muscle. There were no metastases. Recently a third case of leiomyosarcoma of the esophagus associated with a diaphragmatic hernia has been described in the Case Records of the Massachusetts General Hospital (7). Mallory says the tumor mass was found in the terminal portion of the esophagus, stopping absolutely short at the cardia. There was metastasis to a group of mediastinal lymph nodes on the anterior surface of the esophagus just behind the pericardium. The histological description of the tumor is not given. In view of the fact that leiomyosarcoma of the upper one-third of the esophagus is extremely rare, it seems justifiable to present the following case.

CASE REPORT

A white painter, aged 38, was admitted to the hospital on January 18, 1936, complaining of inability to swallow

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‡Received September 23, 1936.



Fig. 1. Autopsy No. 28-4-36. Photograph No. 1. Reproduction of the X-ray showing the peculiar distribution of the barium in the esophagus.

solid food and loss of eighteen pounds in weight in the past year. He stated that in 1929 he had first noticed a soreness in the right side of his throat, associated with some pain on swallowing and with a bad odor coming from the mouth. He added that in the past year there was increased difficulty in swallowing and that for two months he had been unable to swallow anything but liquids. For some time he had been unable to clear his throat and had expectorated small amounts of dark brown material, but there had been no regurgitation of food or blood. The past history, except as related to the present complaints, was unessential.

The patient had been seen early in 1935 by Dr. T. M. Joyce of Portland, Oregon, when *Radiographic studies* of the esophagus showed it to be dilated above the level of the second dorsal vertebra and the patient was noted to have difficulty in swallowing barium. An *esophagoscopic examination* was therefore done and a biopsy made. Definite malignancy, either an anaplastic carcinoma or possibly a sarcoma, was reported by the pathologist. A few days later the esophagus was exposed through the neck and 30 mg. of radium were implanted in the tumor wall and allowed to remain for ten hours. There was improvement for some time, and the patient had less difficulty in swallowing. The patient was also stated to have been given X-ray treatments by another physician in June, 1935.

Physical examination revealed a white male weighing 120 pounds. In the neck there was a sausage-shaped swelling beginning just below the larynx and extending beneath the sternum. This mass was firm, hard but not tender. On the skin surface to the right of the midline the healed incision of the previous radium implantation was seen. There were no other essential findings on physical examination. *Laboratory studies* showed the urine and blood to be negative. The white count ranged from 9,000 to 11,600, and the neutrophilic forms ranged from 85% to 90%. During his stay in the hospital the patient's temperature ranged from 36.0 to 37.6. *Radioscopic and radiographic studies* of the esophagus on January 23, 1936, showed the barium to spread out in an unusual manner, irregularly filling the upper portion of the esophagus. A narrowing of the lumen was observed at the level of the sixth cervical vertebra, not sufficient, however, to prevent the rapid passage of the barium to the level of the aortic arch where another narrowing was seen. Between the two constrictions a considerable degree of widening of the esophagus was observed. Below the arch, the barium proceded rapidly to the cardiac orifice where there was evidence of slight spasm which quickly relaxed, permitting fairly rapid passage of the barium into the stomach. (See radiographic reproduction No. 1. Dr. Bloom, V. F., Portland, Oregon).

Because of rapid recurrence after previous high voltage therapy, irradiation of the tumor mass was not considered at the time of entrance. A gastrostomy was done (Dr. Peiffer, G.) on March 9 for the purpose of conserving the patient's strength and for palliation. Following the gastrostomy the neck was cautiously irradiated, small dosage being employed to prevent edema of the glottis. On March 18 the patient complained of pain in the neck, which was swollen, red and indurated on the right side.



Fig. 2. Autopsy No. 28-4-36. Photograph No. 2 illustrating the massive fungoid growth which occupied the upper end of the esophagus, projecting upward into the pharynx. Note the base of the tongue at the top of the photograph at "T"; the hemorrhagic, necrotic mass at "H."



Fig. 3. Autopsy No. 28-4-36. Photograph No 3 of a sagittal section made through the tumor mass. "T" tongue; "E" probable area of origin of the tumor with extension forward into the trachea; "H" hemorrhagic mass projecting downward in the esophagus.

Several days later an abscess of the neck was opened and drained. Following this flare-up the dysphagia gradually increased. On April 19 there was considerable bleeding from the throat, and the patient expired two days later.

At the autopsy (F.R.M.) the body was seen to be that of an emaciated white male. The neck was asymmetrical with the presence of a roughly nodular swelling on the right side, lateral and inferior to an old healed scar extending from the sternal notch upward along the anterior *border of the right sternocleidomastoid* muscle. The left side of the neck showed some rather diffuse swelling but no other abnormality. The gastrostomy wound was found to be normally functional. When the neck was opened a mass of extremely friable, bloody, necrotic tissue, in which were large nubbins of whitish tissue, was found in the posterior pharynx. (See photograph No. 2). This mass was continuous with a larger mass completely occluding *the laryngopharynx and esophageal lumen*. Examination of the mass revealed it to consist of a whitish, firm, papillomatous growth attached to the anterior wall of the pharynx and to the right lateral wall of the esophagus in its first 10 cm. (See photograph No. 3).

There was a good deal of hemorrhagic necrosis in this tissue, and an extension of the hemorrhagic necrotic tissue was seen to almost occlude the laryngeal opening. A portion of the growth had also invaded the right side of the epiglottis. In the neck below the lower end of the right sternocleidomastoid muscle the abscess cavity mentioned in the clinical history was found to communicate with the superior end of the esophagus at a point 7.0 cm. inferior to the uvula. The palpable nodule in the neck was found to surround the hemorrhagic abscess cavity and to be composed in part of thyroid tissue. The base of the tongue was uninvolved. There was edema of the glottis with partial closure, although a small lumen measuring 3 mm. in diameter was seen. There was no direct compression of the trachea by the neoplasm. Beneath the pleural surfaces of the lungs were found whitish, hard, *discrete nodules* averaging 3 mm. in diameter and a few somewhat larger nodules were found deeper in the parenchyma of the lungs. There were no other evident metastases.

Microscopic sections taken from various areas of the fungoid tumor mass projecting into the lumen and invading the wall of the esophagus revealed more or less compact areas of cells having spindle-shaped or oval nuclei. The cells had in general a dense, longitudinal arrangement. The nuclei were quite long but relatively narrow and possessed rounded ends. They tended to stain uniformly slightly black, and were granular. The nucleoli were not prominent. The cell boundaries were not well defined, but the staining reaction of the cytoplasm was pinkish. Mitotic figures were infrequent. The tissue in general was richly vascular and there were many areas of hemorrhage throughout it. In certain portions of the tumor there was evidence of dissociation of blood pigments which were found both intra- and extra-cellularly. In the grossly hemorrhagic area there was a recent thrombus formation, apparently occurring in a large sinusoidal vessel. In certain areas the nuclei were widely separated and here there was infiltration of leukocytes, serum and fibrin in abundance. In other areas there was myxomatous degeneration. In the more superficial portions of the tumor there were necroses with heavy depositions of fibrin and secondary invasion of polymorphonuclear leukocytes. However, the stratified squamous epithelium was intact over portions of the tumor except where the invasion of polymorphonuclear cells occurred. In some areas there was also superficial granulation tissue formation projecting beneath the epithelium, which was greatly thinned or eroded. There was no evidence of epithelial cell proliferation. The elongated oval to spindle-shaped tumor cells of one of the *metastatic nodules in the lungs* were similar in appearance to those in the primary tumor. The nucleoplasm was also granular and finely stippled. There were no prominent nucleoli and mitotic figures were not seen. The nodule, which obliterated the atrial openings, was surrounded by histiocytes, monocytes and plasma cells. (See photomicrograph No. 1). The application of differential stains (van Gieson) revealed the predominant cell to be of the nonstriated muscle type.

COMMENT

Clinically, there were some unusual features in this case because of the unusually high position of the tumor mass. Thus there was associated abscess formation in the neck with development of a sinus tract extending from the esophagus through the abscess cavity to the surface through the operative incision. Yet the patient died as the result of hemorrhage from a vascular tumor mass with asphyxia due to aspiration of blood. Such cases as this can only be differentiated from the more common carcinomas of the esophagus by microscopic examination of the tumor tissue, provided representative tissue is secured. The chief symptom in both types of malignancy of the esophagus is dysphagia, and other symptoms are related largely to the obstruction. Although the course of sarcoma of the esophagus is said to be more rapidly fatal than carcinoma, the patient's symptoms began with pain on swallowing, six years before death occur-



Fig. 4. Autopsy No. 28-4-36. Photomicrograph No. 1 of a metastatic nodule in the lung disclosing the characteristic cell type as seen in the original tumor.

red. The early occurrence of pain on swallowing in this case of course suggests the possibility of early diagnosis and possible successful management of a relatively accessible neoplasm of the cervical portion of the esophagus, had the patient been seen in 1929. If there are any characteristics of sarcoma of the esophagus which differentiate it clinically from carcinoma, they are pain and the prominence of signs and symptoms that develop in such malignancies of the cervical portion of the esophagus. The only ray of hope in these cases, as in malignancy generally, is the recognition of the significance of early symptoms and the prompt attempt at treatment, for Von Eicken (8) believes the slow growing spindle cell sarcomas to be operable lesions, and the occasional benign tumors causing symptoms may also be removed.

It need hardly be mentioned that the muscular tissue of the esophagus varies in different parts of the tube. Within approximately the lower half of the esophagus the muscle is entirely unstriated, within the second quarter both striated and smooth muscle appear, while in the first quarter striated muscle almost exclusively is present. The zone of purely striated fibers is said to extend somewhat further in the longitudinal than in the circular layer, but the zone of purely striated fibers within the latter includes only about the first 2.5 cm.

It is therefore not necessary to postulate embryonic rests in the upper esophagus to account for the origin of the tumor we have described. Nevertheless it is possible, as Dvorak (4) believes of the rhabdomyosarcomas of the esophagus, that the smooth muscle sarcomas may arise from undifferentiated mesenchyme displaced when the marked developmental changes occur in the ventral floor of the embryonic foregut.

SUMMARY

The leiomyosarcoma here reported evidently grew slowly and invaded slowly. Its extension into the trachea anteriorly probably resulted in the implantation metastases in the lungs since these secondary growths were found in the vicinity of terminal bronchi. It was spontaneous hemorrhage from portions of the vascular tumor, the blood welling up about the epiglottis and being inhaled, that caused death in this case of an unusual neoplasm in the upper portion of the esophagus.

Foot Note: Published with the permission of the medical director of the Veterans' Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the writers.

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Hodgkin's Disease of the Pel-Epstein Type

By

RALPH W. MENDELSON, M.D.

and

E. E. ROYER, M.D.

ALBUQUERQUE, NEW MEXICO

A CONSIDERABLE literature has accumulated with regard to Hodgkin's disease, but the etiological factor still remains unknown. It would be academic to enter into a discussion regarding the various theories advanced nor have we anything new to offer in the line of pathology.

Our patient is of interest from a diagnostic viewpoint for the reason that it so beautifully illustrates the Pel-Epstein type of the disease. This type first was reported by Murchison in 1870 and more carefully studied by Pel-Epstein and later by MacNalty, who states:

"Following on a period of low pyrexia, or of normal or subnormal temperature, there is a steady rise occupying two or four days to a maximum, which may reach 105°. For about three days the temperature remains at a high level, and then there is a gradual fall by lysis occupying about three days, and the temperature then becomes normal."

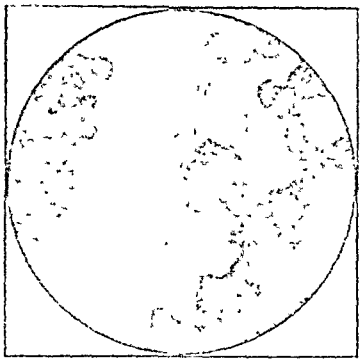
This course usually is followed by an afebrile period of from a few days to one or more weeks when another bout of fever manifests itself. This peculiar type of temperature cycle may be the only manifestation of the disease or may be present with either general or local lymphatic enlargement, such as the cervical, thoracic or retroperitoneal chain. The case here presented is of the latter type, the history being as follows.

CASE HISTORY

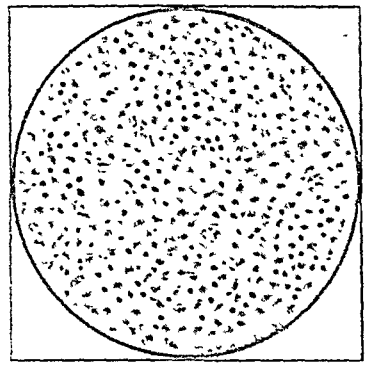
The patient was a white male, age 42, a salesman. His father died at the advanced age of 83 and his mother is living at the age of 72, and affected with the usual disabilities of advancing years. There are four living brothers who are in good health. There are no sisters.

The *past history* includes the usual diseases of child-

Submitted October 11, 1936.



Hodgkin's Disease spleen — Low power.



High power section from retroperitoneal glands showing a few cosinophiles, lymphoid, epithelioid and large multinuclear cells. Hodgkin's Disease.

hood, typhoid fever as a youth, tonsilectomy some few years ago and pulmonary tuberculosis (?) diagnosed ten years ago, but arrested for the past six years.

The *present condition* first manifested itself in the early part of August, 1935, when the patient developed a relapsing type of fever, accompanied by chills and free perspiration. The temperature varied, daily, from normal to 102°. There were no other signs or symptoms of disease and but for the discomfort and weakness incident to the continued abnormal temperature, the patient had no complaints. This state of affairs continued until September 2; then for three days the temperature remained normal, but on September 5 the pyrexia returned and the patient entered the hospital for observation.

The *examination* revealed a man weighing 125 pounds, 5 feet, eight inches in height. The head (including the ears, nose, throat and mouth was negative. The teeth were in good condition. The tonsils were absent. The lungs were normal on physical examination and the X-ray report stated that there was no evidence of recent, or anything to indicate, active trouble. The cardio-vascular and the genito-urinary and neuro-muscular were normal. The skin was without defect. The urine was essentially negative except for a trace of albumen. The white blood-cell count was normal and the differential count was without interest. There were no eosinophiles. Agglutination tests for typhoid, para-typhoid "A" and "B" and abortus-melitensis all were negative in all dilutions.

Symptomatic *treatment* was instituted and the temperature declined to normal on September 11. The patient insisted on returning home on that day where he remained quite well until September 23. Then he experienced a severe chill followed by an acute elevation of temperature. He returned to the hospital and again all laboratory findings were negative. Malaria and relapsing fever were ruled out by careful blood studies. The patient complained of no discomfort except such incident to a sudden rise in temperature. There were no positive physical findings.

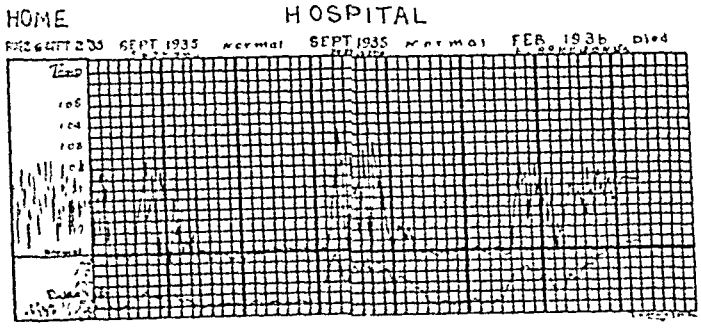
Stool examinations at this time were negative and sigmoidoscopic examination revealed a normal bowel, so far as could be observed. Wassermann negative.

In view of the complete absence of all physical and laboratory findings and the suggestive type of temperature we made a presumptive diagnosis of Hodgkin's disease of the Pel-Epstein type and requested an X-ray examination of the lumbar and pelvic areas in order to visualize, if possible, any glandular enlargement. The report stated that a film taken of the lumbar and pelvic areas, with soft technique with the idea of showing up soft structure in the abdomen in more detail, showed no evidence of pathology.

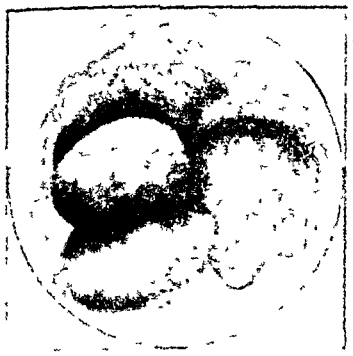
Gastro-intestinal examination was normal except for an unusual spotting throughout the colon, which assumed the form of linear petechia, best seen through the cecum and ascending and transverse colons. The descending colon was well distended and showed normal markings, but also considerable linear petechial spotting. This petechial spotting was reported as indicating an inflamatory condition of the colon, but such roentgen observation was not in accord with the stool and sigmoidoscopic examinations, nor did the patient at any time have symptoms of colonic inflammation.

Careful examination for signs of external glandular involvement was negative; there was no material for a Gordon's test.

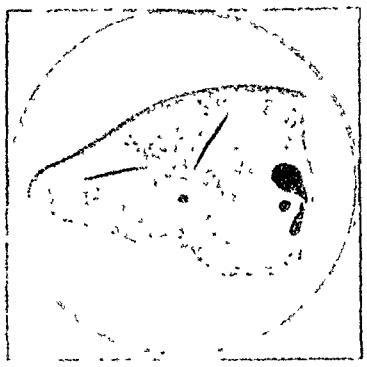
As *treatment*, we exhibited Fowler's solution and by September 28, the temperature was normal and the patient again insisted on returning home. He continued his treat-



Temperature Chart, Hodgkin's Disease. Pel-Epstein type.



Enlarged retroperitoneal glands in Hodgkin's Disease.

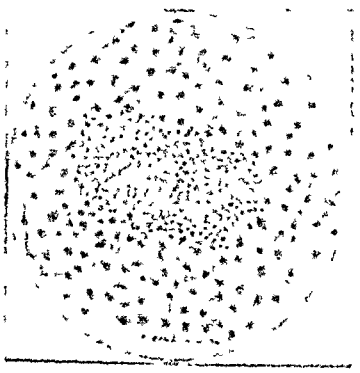


Miliary Hodgkin's of liver.

ment for a short time only. His condition improved noticeably. He was up and around and entered actively into the New Year's festivities. He remained free from any disability until February 6, 1926, when he again experienced a severe chill followed by an elevation of temperature of 105°. He returned to the hospital complaining of intense frontal headache *and was distinctly jaundiced.* The area of liver dullness was distinctly increased, but to what exact extent could not be determined on account of marked abdominal distension. The spleen could not be palpated although the abdominal tympanites did not obliterate dullness in that area. The external glands were not enlarged. The *jaundice gradually increased,* the high temperature with chills and sweats continued and the patient expired February 16, 1926.

Two days previous to death, a single gland appeared in the left inguinal region enlarged to the size of an almond. An *autopsy* was requested and permission granted. The report of Dr. J. R. Van Atta, pathologist, follows:

"The body is that of an adult male about 41 years old, 5 feet, six inches in height; weight about 140 pounds, fairly well developed, but poorly nourished. There is deep general icterus. There are no operative scars. The thorax was opened with the usual incision. Both lungs show the apical adhesions of an old tuberculosis; there are some caseous tuberculous nodules in the apex on the left side. The remainder of the pulmonary area appears normal. The heart and great vessels were not disturbed. No mediastinal glands were noted.



Section from liver — High power Hodgkin's Disease

When the abdomen was opened the liver exhibited a peculiar mottled appearance suggestive of widespread miliary, fatty or amyloid degeneration. The liver was greatly enlarged. The spleen was about twice normal size and showed the same infiltrative process as the liver. The gall bladder was pale and contained mucus. The ducts were all patent. The gastro-intestinal tract was normal grossly throughout. The pancreas appeared to be enlarged. The kidneys appeared normal.

The main pathology in the abdomen consisted of a chain of retro-peritoneal glands which were greatly enlarged, some being hen-egg in size. There were several of these which were matted together with loose fibrous tissue, but the glands themselves were quite discrete. A single almond sized gland was found in the left groin and removed. Section of the retro-peritoneal glands and the inguinal gland show a Hodgkin's disease. The infiltrative spots in the liver consisted of deposits of the typical tissue of Hodgkin's; the same was true of the spleen except the spleen showed considerable secondary infection; the pancreas appeared normal except for some round cell infiltration. The adrenal was normal."

This patient beautifully illustrates a typical case of Hodgkin's disease of the Pel-Epstein type. We do not feel that the old pulmonary tuberculosis in any way affected the picture. We do feel that the presumptive diagnosis was justified in view of the complete lack of laboratory and physical findings in the presence of the characteristic type of temperature curve. At no time during the course of the disease were there any unusual pulmonary, gastro-intestinal, cardio-vascular, genito-urinary, neuro-muscular or other signs or symptoms that might not obtain as the result of attacks of high temperature. The terminal jaundice is accounted for by extensive terminal hepatic involvement; this is not a common finding. The patient made considerable recovery after each period of illness. He suffered no pruritis at any time during the course of his disease.

The illustrations accompanying this report are self explanatory. Special attention is directed toward the liver sections, as they exhibit pathology not common in Hodgkin's disease.

ABSTRACTS

CLINICAL MEDICINE

KISER, EDGAR F., AND ROSENAK, B. D.

Myelophthisic Anemia in a Case of Carcinoma of the Stomach. J. A. M. A., Vol. 107, pp. 963-964, Sept. 19, 1936.

The usual picture of anemia in carcinoma of the stomach is of the secondary type, due to chronic blood loss. In cases in which there is a concomitant achylia gastrica there frequently is a disturbance in hematopoiesis resulting in an anemia of the pernicious type.

A third type of anemia engages our attention at present—a so-called myelophthisic anemia, hemolytic in nature and occurring in diseases which destroy bone marrow. Metastatic carcinoma especially from the breast, thyroid, prostate or stomach is an occasional cause of this type of anemia. It is characterized by a diminution in the red blood cells, low hemoglobin content, marked anesocytosis and poikilocytosis, and a high percentage of polychromatophilic cells and nucleated forms. Myelocytes are frequently found in the circulating blood. Waugh claims that there is an increased fragility of the red cells. Pepper and Forley also say that in the terminal stages there is a complete oplasia of the bone marrow.

The author reports a case treated originally for influenza and tuberculosis which at autopsy revealed an adeno-carcinoma of the stomach with widespread metastasis involving the bone marrow. The blood picture was typical of that described above, except that the fragility of the red cells was normal.

Francis D. Murphy, Milwaukee.

GOLDMAN, LEON

"Gross Hemorrhage from Peptic Ulcer — Its Morbility, Mortality and Treatment." J. A. M. A., 107:1537-1541, Nov. 7, 1936.

This study is based upon a series of 1,025 admissions of 890 patients with peptic ulcer and it includes a seven year period in a charity hospital. The rather irresponsible class of patients affected may account in part for the high incidence and mortality observed in regard to gross hemorrhage, but will probably have little bearing upon the other observations noted.

Gross hemorrhage was the presenting symptom or a development in complication in 38 per cent of the cases and of this group 11.1 per cent died of exsanguination and an additional 4.9 per cent of conditions associated with the bleeding—in other words 16 per cent of those patients having gross hemorrhage died. Fatal hemorrhage usually is caused by erosion of a large artery along the posterior wall of the first or second portion of the duodenum where it overlies the pancreas. This is explained by the fact that these ulcers are less likely to heal than those elsewhere and that with the desruction of the duodenal wall the vessel is surrounded by granulation or scar tissue which has a tendency to hold the artery open and render its walls less elastic.

Exacerbation or recurrence of the symptoms of ulcer usually immediately precedes the onset of hemorrhage. Dietary indiscretion or alcoholic indulgence may have occurred. Nausea is the first system and may be followed by the vomiting of blood and by fainting. Tarry stools occur later but either tarry stools or hematamesis may occur alone, or both may occur, whether the ulcer is in the stomach or duodenum. Shock follows severe hemorrhage and until the fluid volume is replaced blood pressure readings are more accurate than blood counts in estimating the severity of the hemorrhage.

While the rule is quite variable, tarry stools occur more often and hematemesis less often in duodenal ulcers. The incidence of gross hemorrhage reached its peak during the fifth decade, and the mortality was highest in the fifth, sixth and seventh decades when arteriosclerosis is important. In all fatal cases the hemoglobin was below 30 per cent and the red count less than 2 million. The mortality rate showed a definite abrupt rise after the second hemorrhage, and recurrence of hemorrhage is more likely after two have occurred than after the initial hemorrhage.

Treatment consists of absolute mental, physical, and intestinal rest. The patient should be put to bed and given enough morphine to accomplish this. Atropine should be given with the first few doses of morphine to relax the muscularis and inhibit gastric secretion. Blood pressure reading and frequent red counts and hemoglobin determinations should be made. Nothing is given by mouth except alkaline powders. After bleeding has stopped the Sippy regimen can be instituted. During the first 24 or 48 hours parenteral fluids are withheld. Nothing is given intravenously except blood which probably aids in checking hemorrhage far more often than it starts bleeding again. Transfusion is indicated when the systolic pressure is less than 70 mm., the hemoglobin less than 40 per cent, or the patient's general condition such that a second hemorrhage would probably be fatal. Other coagulants or astringents are ineffective. Gastric lavage should be employed only when the stomach is distended with clots. Early surgery is indicated in those patients who continue to bleed or have repeated hemorrhage under adequate medical treatment as described. This is especially true of those in the arteriosclerotic age.

J. Duffy Hancock, Louisville.

SNELL, ALBERT M.

The Effects of Calculous Biliary Obstruction on the Structure and Functions of the Liver. S. G. O., 63:596-603, Nov., 1936.

Accurate estimation of the degree of hepatic pathological and physiological change is not always possible even when the duration and relative completeness of the biliary obstruction present in any particular case is known. This is explained by a number of variable factors: the stones may remain latent, doing damage but not causing symptoms; in different individuals there will be a difference of degree in response of liver tissue to injury; and there is some inconstancy in the interpretation of tests of liver damage.

The pathological lesions following jaundice and common duct obstruction fall into four groups. In the first group which embraces about two-thirds of all the cases, there is a minimal structural change and only slight disturbance of liver function. The cases present only simple uncomplicated biliary obstruction, there is a relatively short history of biliary colic, the jaundice is slight and transient the biliary passages are patent, and the serum bilirubin determination averages about 3 mg. per 100 c.c.

In the second group severe ascending biliary infection plays a major part in the destruction of the hepatic parenchyma, there is a febrile course, the jaundice is deeper and more persistent, intermittent obstruction is quite characteristic, the serum bilirubin varies from 8 to 15, hemorrhagic features and rental insufficiency are common, and there is a frequent associated pancreatitis.

The third group shows an acute or subacute atrophy and degeneration of the liver, an extreme degree of jaundice persists even after the biliary colic subsides and there is increased potency of the biliary passages, the serum bilirubin varies from 15 to 20 mgm., the hemorrhagic tendency is

CONSERVATION OF ESSENTIAL ELEMENTS IN PROTECTIVE FOODS

I. MINERALS

● Considerable differences may exist between the mineral contents of foods from both the qualitative and quantitative standpoints. In fact, variation in mineral content has been noted even in the same plant variety; such variations being dependent, among other factors, upon soil or climatic conditions (1).

A striking example of the influence of one of these factors is the relative richness in iodine of field crops raised in certain coastal regions of this country where the soil is also high in iodine.

From the point of view of those concerned with human nutrition, interest in the mineral content of the food supply is usually centered around calcium, iron and iodine; since it is generally agreed that of all the essential minerals, these are the ones most apt to be inadequately supplied by the average varied diet. Conservation of these minerals in foods is, therefore, a matter of considerable practical interest.

Unlike the vitamins, minerals are not lost during storage of fruits and vegetables. However, solution losses during cooking may be severe, due to the fact that most minerals, as they occur in the plant, are soluble, or at least are extractable, by the water in which they are cooked. For example, cabbage cooked by the usual home method has been shown to lose from 21 to 72 per cent of its calcium (2).

As exemplified by these studies, solution losses of minerals in leafy vegetables are usually high. Losses in vegetables as a class are not, however, so excessive, as indicated by an average reported loss of 19.5 per cent of the calcium in seven common vegetables (3).

The average decrease during cooking in the ash content of five common vegetables has been found to approximate 37 per cent (4).

While the extent of mineral loss during ordinary home cooking methods will vary with the particular element under consideration as well as the food in which it is contained, sufficient evidence is at hand to indicate that such losses may be considerable. It is further apparent that discarding the cooking water—the usual home practice—entails a loss of valuable, essential mineral components of food.

Modern practice in commercial canning goes far in preventing these solution losses of minerals. Canned foods are cooked by the heat process accorded them while still contained within the hermetically sealed can. A minimum of water is used which also remains within the can, conserving for the consumer's use those extractable essential mineral elements which may be lost to the cooking water during home preparation of market varieties of foods.

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(1) 1936 J Nutrition 11, 55.
(2) 1936 J Home Econ 28, 18; 1925 Ibid, 17, 265
(3) 1935 J Home Econ 27, 376
(4) 1917 Amer J Dis Child, 14, 34

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marked, and hepatic insufficiency is apparent.

The fourth group is characterized by either advanced hepatitis with beginning fibrosis or by the development of actual cirrhosis. They develop in individuals having intermittent and incomplete obstruction over a long period of time, the jaundice is slight and constant, the liver and spleen firm and enlarged, but hepatic insufficiency and cholemic bleeding not so common as might be expected. These four groups are not so clear-cut as described and combination forms are often present.

In the latter three groups where there is more or less serious liver damage the metabolic functions as a rule are not greatly disturbed. Estimation of damage must therefore be based upon other functions; the excretory, the detoxifying, and the manufacturing function. Diminished excretion is evidenced by high readings for serum bilirubin and increased urobilinogen in the urine. The detoxifying function is tested by the amount of elimination (in the urine) of hippuric acid following the ingestion of sodium benzoate. An elimination of less than 50 per cent is significant provided renal function is apparently normal. The manufacturing function is concerned with the formation of the blood proteins, fibrinogen, hemoglobin, serum albumin, and serum globulin. Fibrinogen is usually disregarded since it is subject to so many other factors.

None of the hepatic functional tests accurately foretell the tendency to cholemic bleeding. Nygaard's method of determining the plasma coagulability is probably the best test for this.

An interesting tabulation is included.

J. Duffy Hancock, Louisville.



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● Dorst and Morris, Burger and other clinicians have demonstrated the fact that toxic absorption from the intestinal tract may be decreased by the oral administration of Soricin.

When given in adequate amounts over a reasonable period of time, Soricin (capsules or tablets) relieves the many conditions that accompany or result from intestinal toxemia.

Soricin is non-toxic and is not absorbed from the bowel. Large doses have been given over long periods of time without any ill effect.

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INDICATIONS: Bacterial Hypersensitivity of the intestinal tract • Intestinal toxemia • Intestinal allergy • Allergic diarrhea • Urticaria • Angioneurotic edema • Colitis.

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FELSEN, JOSEPH.

The Relationship of Bacillary Dysentery to Distal Ileitis, Chronic Ulcerative Colitis and Non-Specific Intestinal Granuloma. Ann. Int. Med., X, pp. 645-669, Nov., 1936.

Felsen contends that acute bacillary dysentery, acute and chronic distal ileitis, chronic ulcerative colitis and chronic non-specific intestinal granuloma have a common pathogenesis. The study includes 400 cases of acute bacillary dysentery, 29 cases of acute distal ileitis, 22 cases of chronic distal ileitis, 18 cases of combined chronic distal ileocolitis, and 84 cases of chronic ulcerative colitis.

The following data are presented in support of Felsen's contention.

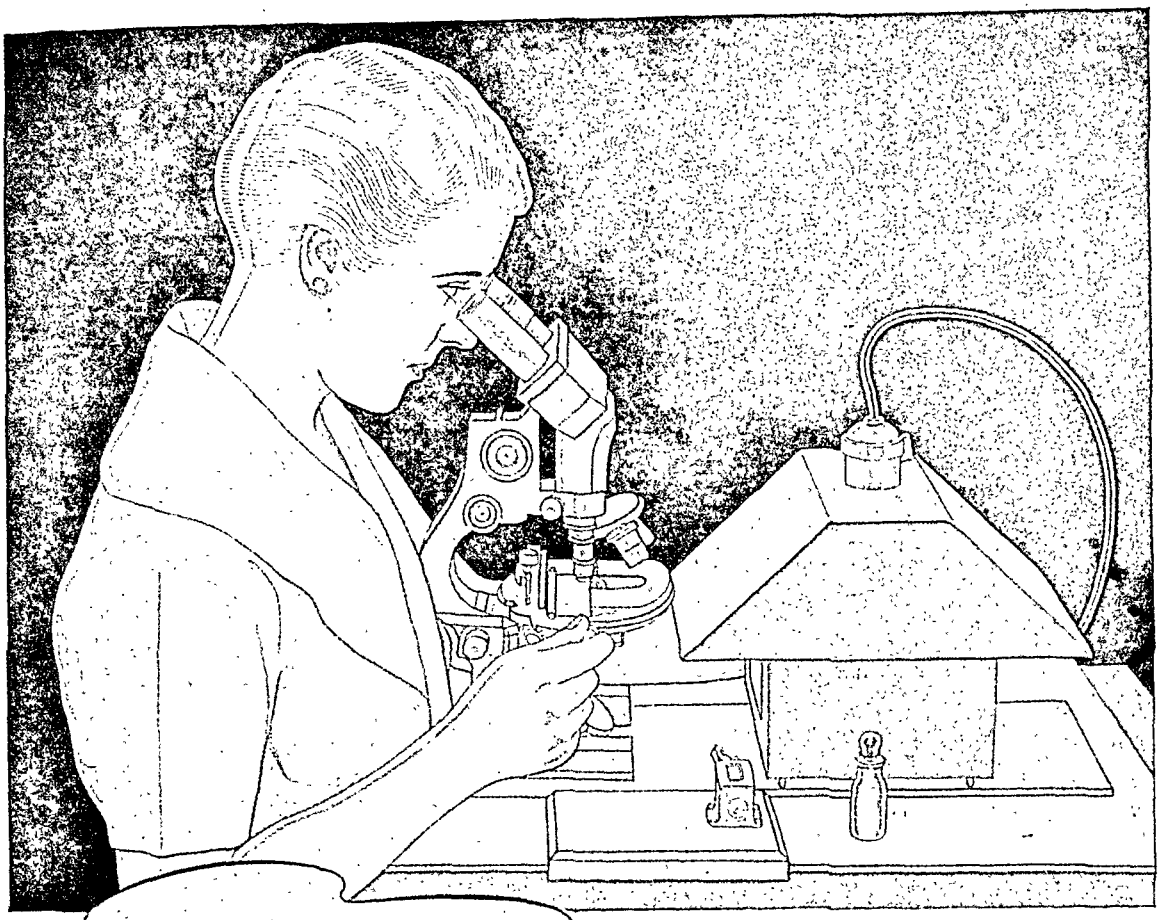
Epidermiological Data.

In the United States the seaport cities are the chief endemic areas for bacillary dysentery. The general geographic distribution of acute distal ileitis, chronic distal ileitis, and chronic ulcerative colitis corresponds to that of bacillary dysentery. Outbreaks of dysentery in the New York area occur both in winter and summer, often in hospitals through improper isolation of unrecognized cases. Contact infection in chronic distal ileitis and chronic ulcerative colitis occurs chiefly during the stage of acute bacillary dysentery when the specific organisms are present in the feces, the incidence being 37.4 per cent in this series of cases. Conjugal infection is relatively common.

Clinical Data.

Acute inflammation of the distal ileum has been noted as an early manifestation of bacillary dysentery and clinically closely resembles acute suppurative appendicitis. A short prodromal period of nausea, headache and moderate pyrexia is followed by pain and tenderness in the right lower quadrant of the abdomen. Generally there is little or no rigidity, but the spastic ileum, or sigmoid may be felt. Felsen has seen acute distal ileitis with mesenteric lymphadenitis in no disease other than bacillary dysentery.

The transition stages from acute bacillary dysentery to chronic ileitis, or ulcerative colitis were noted by a study



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of patients in the Jersey City epidemic, nine to twelve months later. These patients had persistent or recurring intestinal symptoms or signs, namely, diarrhea with blood, mucus and pus; watery diarrhea without gross blood; bloody evacuations without diarrhea, and miscellaneous intestinal disturbances such as recurring attacks of abdominal cramps. In some of the patients, visible evidence was also obtained roentgenographically, sigmoidiscopically, operatively, or at necropsy. In chronic ulcerative colitis, and ileitis "medicants' posture" has been frequently encountered.

The abortive, and atypical types of acute bacillary dysentery encountered recently fall into four groups; the asymptomatic, the meningitic, the appendicular, and the agranulecytoid.

Serological Data.

Diagnostic agglutination titers against B. dysenteriae were obtained in 22 cases of chronic, distal ileitis; 18 cases of combined ileocolitis; and 76 cases of chronic ulcerative colitis, or in 116 (93.5%) out of a total of 124 cases.

Bacteriological Data.

It is generally accepted that positive fecal cultures in acute bacillary dysentery are usually not obtained after the first or second week. In this series 10 out of 70 cases of chronic ulcerative colitis and ileitis were positive for B. dysenteriae. Bacteriophage was found in 20 out of 51 cases, while 100 normal controls showed bacteriophage in only one.

Aspirated fluid from inflamed joints in acute bacillary dysentery, chronic ulcerative colitis and ileitis has proved persistently negative upon culture.

Pathological Data.

In acute bacillary dysentery every case studied showed recto-sigmoid involvement. The earliest lesion is a hyperplasia of the solitary acuminate lymph nodules in a multiple and punctate fashion. There is an acute diffuse inflammation of the mucosa which is covered with a mucoid, blood tinged or purulent exudate. Bleeding occurs after the slightest trauma. Follicular necrosis quickly ensues and in severe cases the entire lymph nodule is eventually destroyed.

From the follow-up figures of the Jersey City epidemic 10 per cent of the cases had reached what Felsen calls the chronic phase of the disease. The ileum and colon show essentially the same pathologic process which is one of mural fibrosis and lymph nodule destruction. Here and there islands of mucosa remain intact and due to the blockage of ducts take on a polypoid appearance. A granulomatous lesion represents a productive type of inflammation. In general, the end-result is an ulcerated, narrowed, thickened, infected, vascularized tube of connective tissue.

Roentgenological Data.

Roentgenographic evidence of chronic ulcerative colitis or ileitis was obtained in 48 cases examined.

Felsen concludes his article with a discussion of the diagnosis and the therapy in acute and chronic bacillary dysentery. This is an unusually able study, well written, well illustrated and is worth reading in toto with care whether or not the reader agrees fully with the views of the author.

B. B. Vincent Lyon and
C. F. Wirts, Jr., Philadelphia.

McGIBBON, J. E. G.

The Clinical Manifestations of the Spread of Carcinoma of the Esophagus Observed During Life. Brit. Jour. Surg., 24:86-104, July, 1936.

The author observed 100 cases of carcinoma of the esophagus over a period of seven years. The study included carcinoma located definitely in the esophagus and did not include growths in the postcricoid area or at the gastro-esophageal juncture.

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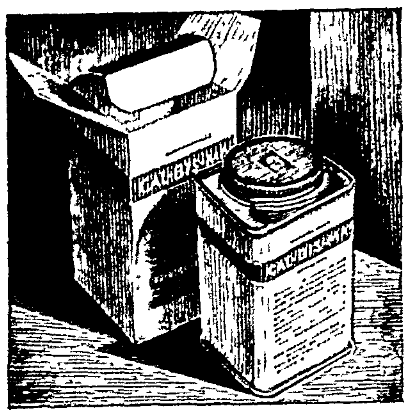
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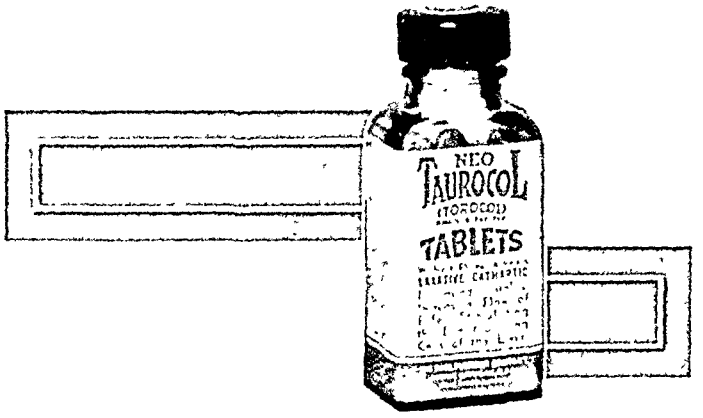
In ninety-one of the patients dysphagia was the first and outstanding complaint; in four, the chief complaint was pain and in one, hoarseness. Two patients came for examination because of impaction of a foreign body in the stricture, and one patient sought medical advice because of enlargement of the cervical glands; in another, hiccough was the presenting complaint. The average duration of symptoms in the entire group was 3.4 months.

Twenty-nine patients showed clinical evidence of extension of the growth at the time of the first examination. Thirteen had paralysis of one of the recurrent laryngeal nerves; in eight, the left nerve was involved; in four, the right and in one case both nerves were paralyzed. The patient with hiccough was considered to have involvement of the phrenic nerve. Three patients showed involvement of the trachea without perforation, and in one a fistula was present. In four cases there were secondary implants in the esophagus. In other cases evidence of extension was present in the intercostal nerves and vertebrae, thyroid, pleura and pelvis. Thirteen of the series had postmortem examination and in ten of this group gross involvement of the lymphatic glands was demonstrated in the thorax or abdomen. Only one patient in the entire series was considered operable, but at the time of exploration the growth was found to be too extensive for removal.

The duration of esophageal carcinoma is divided into three periods: (1) the latent period, from the onset of the lesion until the beginning of symptoms, which is of unknown length; (2) the symptom period, from the onset of symptoms until the diagnosis is made, and in a group of cases selected from the literature this was found to be 5.7 months; (3) the manifest period, or that interval between the time that the diagnosis is made and the death of the patient, which was found to be 5.14 months.

A plea is made for early diagnosis in the hope that if the disease can be diagnosed at the beginning of the "symptom period," successful surgical removal of the growth may be accomplished.

Porter P. Vinson, Richmond, Va.



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EXPERIMENTAL PHYSIOLOGY

DUFF, G. LYMAN.

The Nature of Experimental Cholesterol Arteriosclerosis in the Rabbit. Archives of Pathology, 22:2-161, Aug., 1936.

The author records the data from the study of a further series of experiments with cholesterol-fed rabbits which add much to the growing belief that the role of cholesterol in experimental cholesterol arteriosclerosis is a sequence of pre-existing primary lesions in the media and intima of the vessel wall. The presence of the primary lesion, as yet of unknown cause, permits a subsequent deposition of lipoids within and about it. The article should be read in conjunction with the former paper on "Experimental Cholesterol Arteriosclerosis and its Relationship to Human Arteriosclerosis," Archives of Pathology, 20:81 and 259, 1935 (reviewed in this Journal January, 1936).

Distinctly primary lesions in the ground substance of the intima are recognized in some instances before the deposition of any lipoid substance, and independent of similar lesions in the media. And of greater importance is the recognition of similar primary lesions in the media without corresponding change in the intima. In the media focal destruction of muscle fibres is observed prior to the accumulation of lipoids in the damaged areas. Arterial injury is looked upon as the initial event, and deposition of lipoids



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as a subsequent one. Experimental injury of the walls of arteries by Scolowjew has demonstrated that this may be the case. By cauterization and by mechanical injury of segments of arteries in cholesterol-fed rabbits a more rapid deposition of lipoids takes place than in other parts of the vessels.

The importance of these observations in relation to the etiology and pathogenesis of human arteriosclerosis lies in the significance of focal injury to the wall of the artery by way of the vaso vasorum. The causes of such injuries may not be known now—but they may be assumed to be varied—mechanical, chemical, infection, etc. In the opinion of the reviewer this conception of the mechanism of arteriosclerosis meets the varied known factors of the disease much more logically than does the theory that it is the result of the primary effect of infiltrated lipoids from the blood stream through the intima.

N. W. Jones.

BEAZELL, B. S., AND IVY, A. C.

Chronic Gastric Ulcer Following Bilateral Vagotomy in the Rabbit and in the Dog. Archives of Pathology, 22:2-213, Aug., 1936.

Bilateral subdiaphragmatic vagotomy was performed on thirty rabbits. Twenty-nine rabbits survived the operation and were fed a roughage diet. Twelve of the rabbits developed typical chronic gastric ulcer. Of the animals surviving fifty days, 50 per cent had ulcer. They occurred uniformly along the lesser curvature between the incisura and the pyloric sphincter.

Nineteen vagotomized rabbits living on a smooth diet presented ulcer in but three. That is, the soft diet decreased the incidence of ulcer by about one-half. As cutting the vagi produces gastric stasis, the additional factor of rough food with its attending mechanical trauma is another cause; though, the authors state, not the sole cause. The other factor is unknown.

Ulcer did not occur in sixty dogs which were subjected to bilateral vagotomy above the diaphragm and fed a soft diet. Meek reported the occurrence of two instances of gastric ulcer in thirteen vagotomized dogs fed on dry dog biscuit. Gastric stasis and trauma are therefore considered to be etiological factors in the development of ulcer in these animals.

N. W. Jones.

Lesions in the Pancreas and in the Anterior Hypophysis with Fatal Acidosis Following Prolonged Intravenous Administration of Glucose (In Dogs). Amer. Jour. Phys., 116, No. 1, 194-209, June, 1936.

Dogs were injected continuously with concentrations of approximately 50% glucose at the rates of .7-1.5 grams of glucose per kilogram per hour. Water was allowed ad libitum. Glucose utilization was estimated, and total urinary nitrogen, and carbon dioxide combining power of the blood. At death, which occurred in all cases, postmortem and histological changes were noted. They divide the course of the animal reactions into three phases: the first, without symptoms, of longest duration, in which animals appeared normal, associated with increased urinary nitrogen output, increasing glucose utilization, and slightly decreased carbon dioxide combining power; a second stage in which the animals showed weakness, restlessness, maximum glucose utilization, gradually diminishing carbon dioxide combining power, and nitrogen excretion; a third stage of stupor and coma followed by death, marked acidosis, and failure of glucose utilization. Pathological changes noted were chiefly hyperemic and congestive changes throughout the body tissues; the pancreas and hypophysis being markedly affected by this

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LYMPHOSARCOMA OF THE STOMACH - - - - - - - - - - *E. N. Collins, M.D., and M. G. Carmody, M.D.*

INTRAVENOUS GALACTOSE LIVER FUNCTION TEST - - *I. R. Jankelson, M.D., M. Segal, M.D., and M. Aisner, M.D.*

THE COMPOSITION OF HUMAN GASTRIC JUICE SECRETED IN RESPONSE TO HISTAMINE ADMINISTRATION - - - *C. Gwendoline Toby, B.A.*

DOES HISTAMINE STIMULATE THE SECRETORY ACTIVITY OF THE PEPTIC CELLS IN MAN? - *C. Gwendoline Toby, B.A.*

GASTRO-INTESTINAL STUDIES. VI. THE VOLUME OF THE GASTRIC JUICE IN PERNICIOUS ANEMIA - *Paul J. Fouts, M.D., O. M. Helmer, Ph.D., and L. G. Zerfas, M.D.*

STUDIES ON THE CHEMICAL NATURE OF THE INTERACTION BETWEEN THE INTRINSIC AND EXTRINSIC ANTIANEMIC FACTORS UPON INCUBATION OF LIVER EXTRACT AND NORMAL GASTRIC JUICE - *O. M. Helmer, Ph.D., and Charles P. Emerson, Jr., B.S.*

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THE SIGNIFICANCE OF THE ICTERUS INDEX IN PROCTOLOGICAL DISORDERS - *J. Gerendasy, M.D., and R. V. Gorsch, M.D.*

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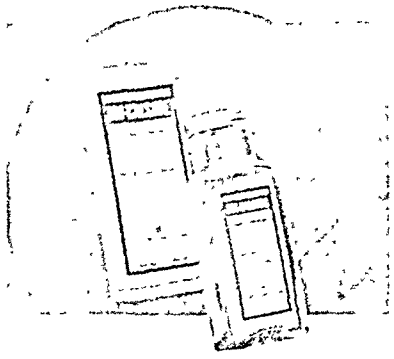
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change, hyperemia of the pituitary was chiefly limited to the anterior lobe. The pancreas in most cases showed engorgement, and gross hemorrhages. The liver showed enlargement, hemorrhages in the parenkyma and marked glycogen storage. Glucose administration caused death in all cases, even those receiving the minimum dosage. The pathological changes were roughly proportional to the quantity and rate of glucose administration.

I. S. Cherry, Chicago.

NECHELES, H., LEVITSKY, P., KOHN, R., MASKIN, M., AND FRANK, R.

The Vasomotor Effect of Acetylcholine on the Stomach of the Dog. Amer. Jour. Phys., 116, No. 2, 330-336, July, 1936.

Experimental studies were made on the rate of blood flow in the stomach of the dog when perfused with acetylcholine. Three types of preparation were used: isolated stomachs supplied by a perfuser dog; stomachs in situ with innervation intact; and isolated stomachs with metal oncometer. Measurements of blood flow, and motility were made in the same preparations, volume changes were measured separately; acetylcholine was administered by single injection or by continuous injection with the Woodyatt pump. The authors observed diminished blood flow in 63% of the preparations with small doses of acetylcholine, but increased flow with larger doses. This biphasic effect was not due to physiologic rebound as it was constant with continuous injection of acetylcholine. The biphasic effect was not noted in the oncometer preparations, a constant volume increase being noted even with small doses. They conclude that the physiologic amount of acetylcholine is probably approximate in concentration to their "small dosages" of acetylcholine, and may therefore restrict blood flow, thereby being an etiologic factor in peptic ulcer.

I. S. Cherry, Chicago.

APPELY, F. L., AND CARY, M. K.

The Chloride and Alkali Content of the Duodenal Secretions and Their Relation to Gastric Acidity and Emptying Time. Amer. Jour. Phys., 116, No. 2, 337-342, July, 1936.

Experiments were undertaken to shed some light on the factors involved in the regulation of hydrochloric acid in gastric secretion as related to neutralization and dilution by diluting fluid secreted or regurgitated from the duodenum; and the relation of these factors to gastric emptying time. Hydrochloric acid test meals were given containing definite concentrations of determinable substance (glucose, iron, dye or urea) at 15 minute intervals samples were withdrawn and determinations made for total chloride, acid, and the substance indicating dilution, neutral chloride was determined by subtracting total from free, and the alkali and chloride in the diluting fluid calculated by formula. They find that acidity is reduced chiefly by dilution and to small extent by neutralization; rate of reduction of acidity varies directly with emptying rate. The rate of reduction of acidity varies inversely as the concentration of neutral chloride and alkali in the diluting fluid. They conclude that acidity depends on the character of the diluting fluid, and that necessarily fluid regurgitating from low in the duodenum and jejunum leads to low acidity, the process being reversed in high acidity.

I. S. Cherry, Chicago.

THIESSEN, N. W.

The Vascularity of Benign and Malignant Lesions of the Stomach. A comparative study with clinical correlations. S. G. O., Vol. 63, No. 2, pp. 149-156, Aug., 1936.

The author, wishing to throw some light on the so-called vascular theory of the causation of ulcer and carcinoma of the stomach, studied 57 resection lesions using histologic methods and methods of injection.

All blocks taken for study were cut in the same manner and compared with sections taken from normal areas of the same specimen. A number of specimens were injected with mercury and roentgenograms made of their vascular patterns. Indices of the vascular density of the specimens were determined and studied in relation to each other and in relation to mortality. In the benign ulcers it was found that the vascularity of the tissue near the lesion was half again as great as in the rest of the stomach. In the case of the carcinomatous lesions the data is suggestive that the patients who lived longest had the more highly vascular lesions.

The author comments that the gradation of vascularity from normal tissue up through benign lesions to fully developed carcinomata does mean something. He suggests that the increased cellular activity in such lesions, and the increased metabolic rate as Warburg contended, requires a greater blood supply.

An appendix, a bibliography, two tables, and five figures accompany the article.

Nelson M. Percy, Chicago.

An Aseptic Method of Temporary Valvular Enterotomy. S. G. O., Vol. 62, No. 6, pp. 1006-1009, June, 1936.

The author describes an aseptic method of temporary valvular enterotomy using a metal tipped rubber tube. The metal tipped rubber tube is fitted with an obturator with a cutting point.

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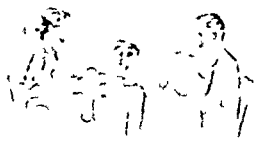
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The author advises a technic in which the tip of the tube is buried against the bowel wall and fastened in place by means of two concentric sutures around the site chosen for the enterostomy. The cutting point of the obturator is then forced through the bowel wall and retracted again into the rubber tube. The tube is now pushed through the opening by a rotary motion and covered over by folds of bowel wall following the method of Witzel over a distance of from 3 to 5 cms. This position of the bowel is now secured to the parietal peritoneum with a layer of omentum intervening, and the tube is placed in the lower angle of the wound. The wound is closed with interrupted sutures and the tube fastened in place by means of a snubbing stitch.

Seven figures and a bibliography accompany the article.

Nelson M. Percy, Chicago.

NUTRITION

SHAPIRO, A., AND KOSTER, H.

The Influence of Bile on the Excretion of Sterol in the Feces. Amer. Jour. Phys., 116, No. 2, July, 1936.

These authors studied the excretion of ether soluble material and determined sterols in the unsaponifiable fraction by digitonin precipitation, in the stools of two patients having "T" tubes in the common bile duct such that the bile could be admitted to the intestine, or excluded at will. They found that total ether soluble substance was increased to 3-4 times the normal when bile was excluded from the intestine. These findings are consistent with those of other investigators. Sterols were increased over the intake value in all cases, whether bile was present or absent in the intestine, but was diminished in the absence of bile as compared to control periods when it was admitted to the intestine; this is in contrast to the findings of Sperry in dogs. The authors conclude that sterol excreted in the feces is greater in human subjects when bile is present in the intestine than when it is excluded, and that this finding may vary from those observed in dogs due to a greater cholesterol content in human, than in dog bile.

I. S. Cherry, Chicago.

SVIRBELY, J. L., AND KENDALL, E. C.

Vitamine C and the Adrenal Cortical Hormone. Amer. Jour. Phys., 116, No. 1, 187-193, June, 1936.

An attempt was made to show the relation between vitamine C and adrenal cortical hormone, in the prevention of scurvy in two adrenalectomized dogs, and in guinea pigs. Nitrogen balance studies were made on two adrenalectomized dogs on a vitamin C free diet and maintainance dosage of cortin. These animals failed to develop scurvy in 106 and 230 days respectively. Variations in nitrogen balance appeared due to inadequate cortin dosage. In guinea pigs on vitamin C free diet, adrenal cortical hormone failed to prevent or cure scurvy.

I. S. Cherry, Chicago.

GRAY, J., KIM, M. S., AND IVY, A. C.

Is a Portion of the Pancreatic Secretory Response to a Meal Due to the Absorption of Digested Food Products. Amer. Jour. Phys., 116, No. 1, 210-213, June, 1936.

In an experimental study to determine the effects of split-protein products; dextrose, and emulsified fats, on pancreatic secretion in acute and chronic pancreatic fistula dogs; these substances were injected intravenously after adequate control periods, and the secretory response checked by threshold doses of secretin. As protein split-products, liver extract (fraction active in pernicious anemia) and Witte's peptone were used. The liver extract, with vasodepressin substance removed, produced no secretory response. Witte's peptone intravenously caused slight temporary increase in secretion, but after 20-30 minutes the pancreas became refractory to further large doses, though the response to secretin was augmented. No response was observed on introduction of these substances into the intestine. Dextrose and emulsified fats produced no secretory response. It was concluded that secretin appears to be the sole humoral excitant of pancreatic secretion following a meal.

I. S. Cherry, Chicago.

ROENTGENOLOGY

YATER, WALLACE M., OTELL, LAURENCE S., AND HUSSEY, HUGH H.

Hepatosplenography with Stabilized Thorium Dioxide Sol: A follow-up study of 200 patients examined over a period of five years. Radiology, 27:4-391, Oct., 1936.

This valuable article deals with 200 patients examined over a period of five years. The amount of solution administered in the average case contained a quantity of thorium dioxide equivalent in alpha-ray activity to from 1.5 to 3.0 micrograms of radium. The beta-ray and gamma-ray activity is probably insignificant. After a period of five years it is evident that a large amount of the metal remains present in the body, but some of it is mobilized from the original reticulo-endothelial cells in which it was deposited. The dose for each pound of body weight at present used by the authors is 0.5 c.c. of the stabilized colloidal solution of thorium dioxide containing approximately 22% of metal by



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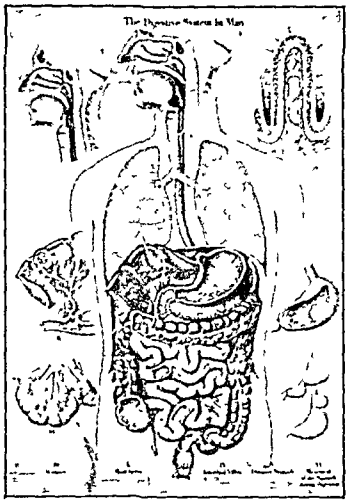
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volume. One-third of the total dosage is usually injected intravenously on each of three successive days, and films made thereafter on the fourth or any successive day.

The useful objects of the test are as follows: (1) In determining the nature of a mass in the upper part of the abdomen. (2) To determine the presence and kind of hepatic disease (atrophic cirrhosis, hypertrophic cirrhosis, syphilis of the liver, metastatic malignant lesions, primary tumor, abscess, cyst, and amyloidosis). (3) To ascertain whether metastatic lesions are present in the liver if operation is contemplated for carcinoma. (4) To demonstrate rupture of the liver or spleen. (5) To determine the cause of jaundice (whether intrahepatic or due to obstruction of the common duct). (6) To follow the progress of hepatic or splenic disease. (7) To demonstrate whether a lesion is above or below the diaphragm. (8) To diagnose ascites.

There are no contraindications established as yet for the procedure. No reactions have occurred. No harm has been observed in the liver even in cases of acute hepatitis. Of the 200 cases, the diagnosis was proved in 73 cases. The diagnosis by hepatosplenography was correct in 67 cases; incorrect in 6. Of the 6 incorrect diagnoses, 4 had metastatic lesions in the liver which were unsuspected in spite of the procedure, in another case primary carcinoma was diagnosed as metastatic carcinoma, and in one case cirrhosis of the liver was not diagnosed.

Stated in other words, out of the 200 cases the clinical diagnosis was confirmed in 61; the diagnosis was made from the hepatosplenograms in 49 cases; the procedure was used to eliminate or to establish the presence of metastases in 46 cases; and it was of negative value in 35 cases; wrong in 6 cases. The majority of the 200 patients were suffering from some fatal malady. Of 47 who are still living, 11 have had the thorium between three and four years, and 14 between four and five years. The first patient injected is still living and well, in spite of a chronic leukemia. Of the 47 patients known to be living, 36 have been reexamined either at intervals or within very recent date. A number of them were cases of cirrhosis of the liver, but clinical studies, including the bromsulphthalein test, have showed markedly *little progression in the severity of the* disease in most cases. There has been no increase in susceptibility to infection. A preliminary histopathologic study in 71 cases indicate that the presence of thorium dioxide has not caused appreciable organic changes. The authors predict that hepatosplenography with stabilized thorium dioxide sol will come to be recognized as an essentially harmless diagnostic procedure.

James T. Case, Chicago.

MERRITT, E. A.

Radiation Therapy of Inoperable Intra-abdominal Malignancy. With special reference to the stomach. Amer. Jour. Roent., 36:3-324, Sept., 1936.

Sporadic attempts at roentgen treatment of inoperable gastric cancer have been reported since 1903. The author has advocated pre-operative irradiation of obscure abdominal tumors for some years and has never observed that it delayed or prevented recovery. On the other hand, he states that he has proof of its very great value as a life giving measure. Now that the fractional method of Coutard or its modification is coming into general use, malignant newgrowths of the stomach as well as other suspected intra-abdominal tumors should be treated with roentgen irradiation when operation is not available. If the lesion is resectable, Merritt does not advocate irradiation. Case reports are published concerning four patients.

James T. Case, Chicago.

JORDAN, S. M.

A Review of the Gastric Ulcer Problem. J. A. M. A., 107:1451, Oct. 31, 1936.

In this study 119 cases have been used in which the diagnosis of gastric ulcer had been made and checked either by surgical exploration or by follow-up studies varying from a few months to eleven and one-half years after medical treatment. Sixty-two of the cases were men and fifty-seven were women.

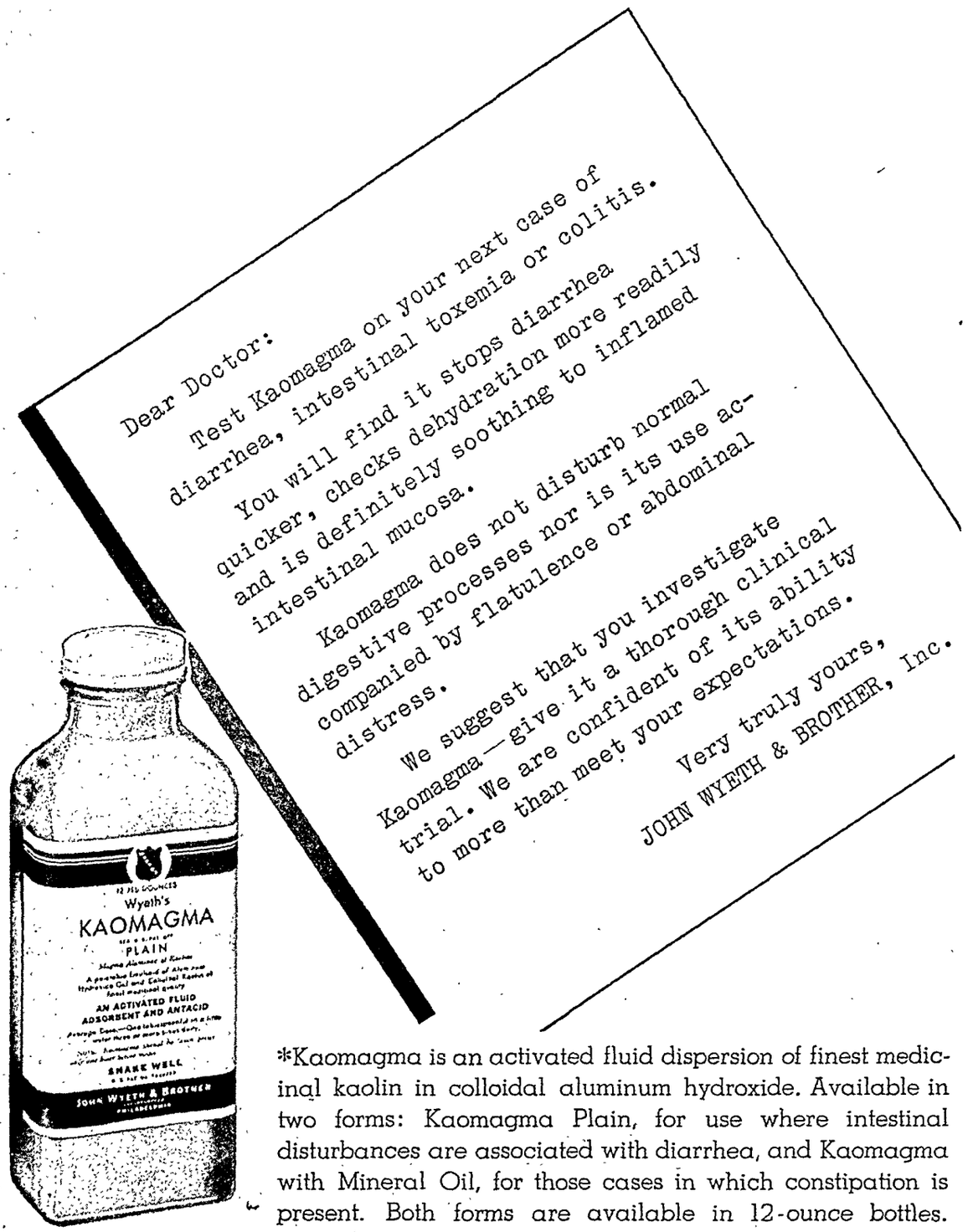
The first question which arises upon X-ray examination is, is the lesion organic? Spasm, adhesions, cicatrization of an old lesion, and a loop of small intestine distorting the stomach may cause confusion. A prepyloric constriction is the most likely to cause trouble, simulating an annular carcinoma. It may occur independently or with cholecystitis, appendicitis, duodenal ulcer, or an ulcer of the middle of the stomach. It can be relieved by ulcer therapy or treatment of the underlying cause. Sometimes after its relief the real lesion is found in the duodenal cap, while other times the true cause is not known.

Adhesions may so deform the stomach that it may be difficult to determine whether the lesion is a malignancy, an old lesion, or a new one. In some cases of this series an hour glass deformity was found, which at operation turned out to be adhesive bands around the middle of the stomach, or the cicatrix of a posterior wall ulcer.

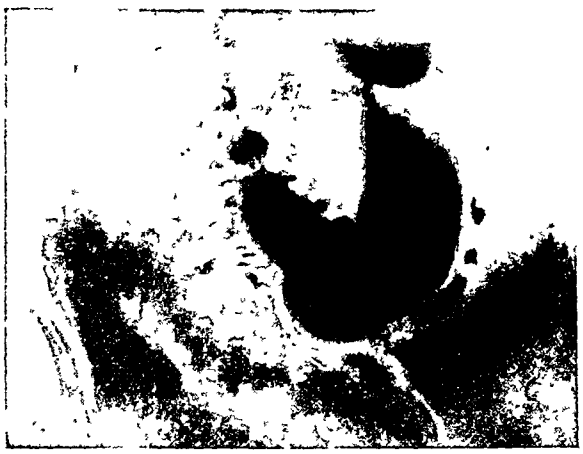
The silhouette of a loop of jejunum or the third part of the duodenum against the lesser curvature may give the appearance of an irregular area which resembles a carcinoma or an ulcer with a smooth crater.

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The next question which arises is, is the lesion benign or malignant? This can be answered by the history, by gastric analysis and by X-ray examination. The history must consider the duration of symptoms and any recent changes of symptoms, the absence of food relief and the frequency of vomiting, loss of appetite and weight. Gastric analysis usually shows no acid in malignancy while in ulcer there is acid present.

In the X-ray study of the lesion the original appearance of the lesion must be studied and the changes it undergoes under trial treatment. The ulcer is considered healed only when the crater completely disappears. The ulcer of the pars media, lesser curvature, is usually benign, while the less common prepyloric lesion and lesion of the posterior wall are more likely to be malignant.

In order to safeguard against a present malignant condition or future malignant condition the management must be limited in time and careful follow-up studies must be made. The complete disappearance of the ulcer requires three to eight weeks and sometimes in lesions of the posterior wall even longer.

The question of surgical intervention can be answered by saying that where malignancy is suspected, or where it is thought recurrence may take place with possible malignant degeneration, surgery should be done.

After healing of the ulcer it has also been observed that those patients who live carefully are not as prone to recurrences as those who do as they please.

Francis D. Murphy, Milwaukee.

BEST, R. R., AND HICKEN, N. F.

Cholangiographic Demonstration of Biliary Dyssynergia. J. A. M. A., 107:1615, Nov. 14, 1936.

In this paper the authors present clinical and X-ray evidence of spasm in the lower end of the common duct They also discuss their work in injecting radiopaque substances into the common bile duct during operation. The solutions they have used for this are lipoiodine, tharium dioxide solution and hippuran in 48 per cent aqueous solution. Immediately after the injection of the fluid roentgenograms are taken. If it is believed necessary they are repeated later and have been found valuable in ascertaining why biliary fistulae fail to close, or spasm of the common duct.

The authors believe immediate cholangiography at operation to be of value in demonstrating common duct stones which may not be palpable, in diagnosing pancreatitis or tumors of the head of the pancreas, and to determine the patency of the cystic duct.

In addition the authors attempted to verify the idea that some cases of gall bladder colic were due to spasm of the sphincter of Oddi. They did this by injecting, postoperatively radiopaque substances into the bile ducts either through a catheter left in the cystic duct, in the common duct, or a T tube. They found this spastic biliary dyssynergia to exist in 15 per cent of 75 cases.

The spasm of the sphincter was sometimes relieved by the injection of the warm opaque substances. They also found that glyceryl trinitrate tablets, magnesium sulfate, atrophine, belladonna, cream, and olive oil relieved the spasm.

Francis D. Murphy, Milwaukee.

SURGERY OF THE LOWER COLON AND RECTUM

SWEIG, WALTER.

Diseases of the Rectum. Rev. of Gastroenterology, 3:3, 251-8, Sept., 1936.

Hemorrhoids, carcinoma, proctitis, and pruritus are discussed.

Bleeding which can be accounted for by hemorrhoids, should not be accepted as such until thorough proctosigmoidoscopic examination for carcinoma has been made

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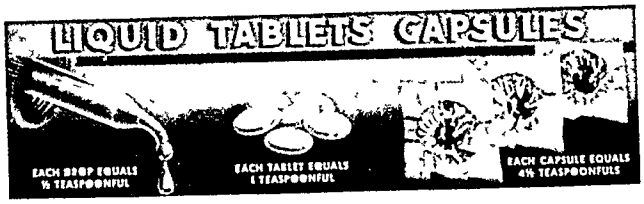
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after careful preparation of the bowel. Hemorrhoids are treated mainly by injection.

A lesion diagnosed non-malignant by a single biopsy examination may prove to be malignant if biopsy is repeated from a different part of the tumor. Schmieden and Westhues believing that all carcinomas of the rectum develop from a polyp regard radical operation absolutely necessary when a polyp is found, whereas the author agrees with Maresch that only seven per cent of polypi degenerate into carcinoma and suggests a proctoscopic examination every three or four months would preclude overlooking a malignant degeneration. Results comparable with the abdominoperineal operation are reported by the sacral method of operation with retention of the anal sphincter. Surgical intervention in the presence of colloid carcinoma is futile. No benefit has been observed from X-ray or radium therapy except in anal carcinoma in which case radium supersedes surgery.

Chronic proctitis is considered one of the most frequent rectal diseases. Four stages are described. They are designated proctitis mucosa, ulcerosa, granulosa, and atrophicans. The granulosa stage represents the healing of the ulcerosa form and proctitis atrophicans is the end stage. *The method of treatment is omitted.*

In anal eczema and pruritus not due to such general diseases as uremia, diabetes, et al, the main etiologic factor is proctitis. The secretion from the diseased mucous membrane is responsible for the skin changes and symptoms. Treatment consists of shaving and cleansing the perianal skin, removing condylomata, applications of silver nitrate or tannic acid solutions to the skin, local treatment of the proctitis, subcutaneous injections of plenocain at the edge of the eczematous area, and oral sedation (translated by Julius Gerendasy, M.D.).

Reviewer's Note:

Whether the opinions expressed in this article are those of an individual or are representative of Europe they are different from those of leading proctologists in this country. As evidence of this divergence of opinion mention may be made of the percentage of malignant degeneration in polypi, the choice and types of operation for carcinoma, the beneficial effects of radiation therapy, views on the subject of proctitis, and results in the treatment of pruritus.

Wayne W. Flora, Chicago.

ROBERTSON, JARRETT P., AND SHARP, LEE.
Granuloma Venereum and Lymphopathia Venereum. Amer. Jour. Surg., 34:2, 322-3, Nov., 1936.

Considerable confusion exists regarding two diseases, granuloma inguinale and lymphogranuloma inguinale, probably largely as a result of the similarity of names and their venereal nature. Granuloma venereum and lymphopathia venereum have been suggested for general use as being more descriptive of the conditions.

"Granuloma venereum is a chronic disease which destroys the skin and subcutaneous tissue, spreads slowly by continuity and contact but does not involve the lymph nodes and deeper structures." The laboratory diagnosis is made by finding Donovan bodies (Gram negative encapsulated bacilli) in epithelial cells removed from the lesion. The clinical diagnosis depends on the history, local examination, and response to specific therapy. It must be differentiated particularly from chancroid, chancre, and sometimes the primary lesion of lymphopathia venereum. The Ito-Reenstierna skin reaction and search for Ducrey's bacillus are commonly used as is the dark field examination. Fuadin gives 40 per cent quicker healing, is less toxic, and allows fewer recurrences than does tartar emetic.

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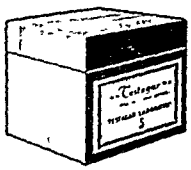
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in diagnosis and is responsible for the rapid progress made in the study of this disease in the last decade. Differential diagnosis includes consideration of inguinal swellings as a result of chancroid, syphilis, tuberculosis, non-specific infection, Hodgkin's disease, and malignant metastases. Fuadin, though not specific, gives better results than any other therapeutic agent.

From the authors' experience in controlling these diseases lymphopathia venereum is considered more contagious and more easily transmitted than granuloma venereum.

Wayne W. Flora, Chicago.

RIDDOCH, J. W.

Anal Fissure. The Lancet, 2:20, 1150-1152, Nov. 14, 1936.

In spite of the fact that fissure is one of the commonest of anal conditions there is a lack of unanimity of opinion regarding its cause, chronicity, and rationale of cure.

According to Ball, fissure resulted from a tearing down of a rectal valve by a scybalum, the valve forming the sentinel pile. As a modification of this theory it was suggested that a small subcutaneous sinus develops following rupture of an anal valve, the fissure resulting from the giving way of the roof of the sinus. The most recent view is that most fissures result from the tearing of a "pecten band" by a hard fecal mass.

Chronicity has been ascribed to spasm, scar tissue formation during attempts to heal recurring tears, and infection.

The upper two-thirds of the anal canal which is lined by mucous membrane is separated from the lower one-third which is lined by skin, by the pectinate line (the level of the anal papillae). The band of skin extending from 3 to 9 mm. below this line has been called "pecten," the "anal intermuscular septum" being firmly attached immediately under the pecten. This septum separates the *internal sphincter muscle from the subcutaneous portion* of the external sphincter and into it is inserted the fibrous prolongation of the longitudinal muscle of the anal canal. The key to this discussion is this septal region. The superficial external sphincter lies outside this ring and is arranged in an elliptical manner, the fibres from each side attaching to the central point of the perineum forming a wide angle and the fibres attaching to the anococcygeal raphe and coccyx forming a sharp angle. The support from this muscle to the septal ring is especially weak posteriorly and less so anteriorly.

The author suggests that trauma such as the passage of large hard scybalae causes rupture of the most rigid part of the canal, the septal region, at the points posteriorly and anteriorly where the support is deficient. The damage may be in the nature of small extravasations of blood followed by fibrous tissue formation and contraction with formation of a ridge of fibrous tissue which ruptures with passage of a hard fecal mass.

Chronicity is due to narrowing of the anal canal at the septal ring produced by contraction of scar tissue and deficient blood supply. Spasm may be of some importance but it is not a decisive factor.

The avoidance of overstretching of the anal canal and increasing the blood supply by stimulating applications or injections are the principles of treatment. The injection treatment may be useful in selected cases but it is not ideal because of increased scar tissue formation, lack of healing even after repeated injections in some cases, and in others persistence of pain with defecation even when healed.

The author's surgical method is commonly used in the office or clinics. The region to be incised is infiltrated with an anesthetic solution. A slotted anoscope is inserted with the slot and fissure corresponding. The anal intermuscular septum is incised while under tension until the

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*Am J Roentgen 19 341 1928 Am J Med Scien 6-182 1931
**Arch Int.Med 38 647,1926 Am J Surg 7 455 1929
***Ann. Int Med 6-1465 1933 J Lab & Clin Med 19.567 1934

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Reviewer's Note:

Three points should be emphasized regarding the pecten as agreed upon by those who have made a careful study of the anatomy of the anus.

1. The pecten is an area of subcutaneous fibrosis which may also involve the overlying skin.

2. It partially surrounds the skin but is not a complete band.

3. It is not constantly present with those lesions with which it does occur.

Wayne W. Flora, Chicago.

PETTIT, ROSWELL T., AND EDGCOMB, J. J.

Critical Analysis of Methods of Treatment of Rectal Carcinoma, Particularly Electrocoagulation. Am. Jour. Surg., XXXIV, 1:57-64, Oct., 1936.

The anatomy, pathology, diagnosis, and management of carcinoma of the rectum are briefly discussed, the management being classified under the following three methods: surgery, radiation, and electrocoagulation.

As a foundation for electrocoagulation therapy three factors are emphasized. First, the fact that carcinoma of the rectum is in most cases within reach of the finger makes it easily accessible for diagnosis and treatment. Second, carcinoma of the rectum metastasizes late. Wood and Wilkey are quoted as stating that spread is chiefly by local continuity and that spread by the blood stream is accidental. The authors state that these findings are in contrast to those of most pathologists who find widespread metastasis to lymphatics, peritoneum, and liver. Third, the five year survival following electrocoagulation compares favorably in the authors opinion with the 38 per cent to 50 per cent following surgery.

This writing covers their experience in the last nine years with 15 cases of carcinoma of the rectum treated by electrocoagulation, radium, X-ray or some combination of these. Colostomy was not used.

Electrocoagulation was used in 13 cases. Of these two were treated by electrocoagulation alone, six with radium and X-ray, three with radium, and two with X-ray. Of the two cases in which electrocoagulation was not used one was treated with radium and X-ray and the other which had been treated elsewhere with radium was treated with X-ray. Further analysis shows that of these 15 cases, two were treated by electrocoagulation alone, two by radiation alone, and 11 with electrocoagulation and radiation combined.

The most common complication following electrocoagulation is rectal stricture. There was one hemorrhage late in the second week and one death on the fifth day due to perforation and peritonitis.

Reviewer's Note:

Electrocoagulation has been widely used in a number of conditions especially in the past few years. In a small series of cases in which radiation therapy has been used in addition to electrocoagulation, the beneficial results of the latter are difficult to evaluate satisfactorily. Up to the present time those surgeons who are generally considered as being best able to give a valuable opinion about therapy of carcinoma of the rectum by their extensive study and experience maintain that the malignant nature of the disease requires wide removal of the lesion and the lymphatic structures which might serve as a means of metastasis.

Wayne W. Flora, Chicago.

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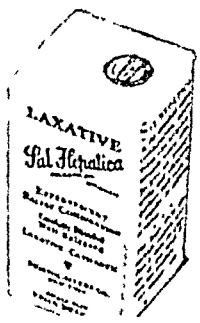
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C. A. Elvehjem,
Am. J. Pub. Health,
25:1334, Dec., 1935.

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SECTION I—*Clinical Medicine: Diseases of Digestion*

The Effect of Administration of Aluminum Preparations on the Secretory Activity and Gastric Acidity of the Normal Stomach*

By
A. C. IVY, M.D., LAWRENCE TERRY, M.S.,
G. B. FAULEY, M.D.
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CHICAGO, ILLINOIS

ALTHOUGH aluminum preparations have been and are being used to some extent in the treatment of "peptic" ulcer in man (1, 2, 3, 4, 5, 6), we have been unable to find a study of the effect of the prolonged administration of relatively large quantities of such preparations on the secretory activity of the stomach of normal subjects. Einsel, Adams and Myers (2, 3) observed that the gastric acidity of ulcer patients was reduced after several weeks of treatment with aluminum hydroxide cream ("Al cream"), although a normal histamine response was obtained. Such a reduction in acidity may be ascribed to several factors, such as: (a) a natural decline of the "abnormally reacting" stomach in consequence of the remission of the ulcer; (b) a decrease in gastric retention as the ulcer enters a remission; (c) the aluminum, because of an astringent action on the gastro-intestinal mucosa, or the coagulation of mucin, or a reduction in gastric digestion, may decrease the secretagogic action of food; (d) the aluminum may cause a mild gastritis. The absorption of aluminum in systemic toxic amounts and an effect on the acid-base balance of the blood has apparently been ruled out (3). Because the possible operation of the first two factors one cannot derive from Einsel's observations what the real effect of aluminum medication on gastric secretion is. This work was primarily undertaken to answer that question.

METHODS

The investigation was conducted chiefly on healthy, vigorous dogs fed a balanced diet ad libitum. Two aluminum preparations were used. One was aluminum hydroxide cream. (In the earlier part of the work the cream was made by us; later we purchased Creamalin (Cleveland Chemical Associates), the buffering action of which was almost the same as our's). The other was Alucol, a colloidal aluminum hydroxide (Wander Co.) in the form of a powder, which was administered with a little water. A few experiments have also been performed on human subjects primarily for the purpose of ascertaining the degree of buffering of gastric acidity obtained with the aluminum preparations.

The capacity of the two preparations to buffer N/10 HCl was determined. Neither was immediately soluble in a large excess of N/10 HCl, Alucol being considerably less so than the Al cream, a factor that is concerned in the interpretation of our results. The samples of the preparations were set aside in contact with excess acid for periods of ½, 1, and 2 hrs., and then back-titrated with N/10 NaOH electrometrically. In order for one to check our results the details of our method of titrating must be given. Samples of 2 c.c. of the Al cream and 1 gram of Alucol powder were used. The samples were placed in 100 c.c. of N/10 at 37° C., the mixture being stirred about ¼ min. every 5 min. At the end of the periods stated, the samples were quickly cooled to room temperature (20° C.), 5 drops of 0.2% Töpfer's reagent were added and the mixture back-titrated with N/10 NaOH. Readings of alkali used were made at three different H-ion concentrations, namely, pH 3.76, or the first indication of change of Töpfer's from the red, at pH 4.0, and at the change of Töpfer's reagent to yellow, or a pH of 4.2. One c.c. of aluminum hydroxide cream buffered at a pH of 4.2, 9.21 c.c. of N/10 HCl in one-half hour, 10.34 c.c. in one hour, and 12.86 c.c. in two hours. One gram of the Alucol powder buffered at a pH of 4.2, 22.18 c.c. of N/10 HCl in one-half hour, 32.87 c.c. in one hour, and 34.97 c.c. in two hours.

The single doses of aluminum cream and Alucol actually used were 20 c.c. and 10 gm. respectively, such relatively large doses being chosen to obtain maximum effects, and to buffer theoretically from 250 to 350 c.c. of N/10 HCl in a two hour period, provided the acid and aluminum preparations were retained in the stomach, which of course, does not happen in vivo. In a one hour period these doses have the potentiality of buffering (pH 4.2) 206 c.c. and 328 c.c. of N/10 HCl respectively. The values for pH 4.2 only are given because we always titrated gastric samples to the yellow color of Töpfer's, an unmistakable end point.

To one group (5 dogs) 20 c.c. of aluminum cream, and to a second group (6 dogs), 10 gm. of Alucol were given four times a day, at 9 a.m. and at 1, 5, and 9 p.m. The dogs were fed at about 11 a.m., excepting on the days that test meals were fed. Medication was continued for more than four months.

Before starting the medication, an index of the secretion of the stomach was obtained (a) by feeding a test-meal and then aspirating a sample hourly for four hours, and also (b) by feeding the test meal three times per day and aspirating the stomach 4 hours after each meal, namely, at 1, 5, and 9 p.m. After starting medication the test meals and aspirations were performed about once weekly. The test meals were given with and without

*From the Department of Physiology and Pharmacology, Northwestern University Medical School, Chicago, Illinois.
Submitted October 29, 1936.

TABLE I

Animals on continuous medication for sixteen weeks

Averages, daily	Before Medication Control		After Medication First 9 weeks		After Medication Last 7 weeks	
	Free	Total	Free	Total	Free	Total
Aluminum Hydroxide Cream						
Plain Test Meals	.069	.220	.07	.23	.07	.20
Medicated Test Meals	.069	.220	.06	.19	.06	.21
Medicated Aspirations	.112	.240	.13	.28	.13	.25
Alucol						
Plain Test Meals	.077	.237	.11	.31	.11	.28
Medicated Test Meals	.077	.237	.05	.18	.07	.22
Medicated Aspirations	.131	.258	.14	.31	.16	.31

aluminum and the four hour aspirations were also made with and without the inclusion of aluminum.

The dose of aluminum was added to the meal; in the case of aluminum cream this was done throughout the period; in the case of Alucol, after several weeks the dogs would not eat their food with Alucol in it, so the Alucol was given by stomach tube, which did not influence the results because the dogs were habituated to taking the tube.

It should be pointed out that the aluminum preparations buffer alkali as well as acid. For this reason, although the values for free acid will be accurate, if much aluminum is present in the gastric sample the total acid value (phenolphthalein as an indicator) will be high. The nature of our results shows that the possible presence of aluminum in our gastric samples did not materially affect the total acid values. However, the greater significance is to be placed upon the free acid values. All titrations of gastric samples were made immediately.

RESULTS

The data are obviously very voluminous and cannot be given in entirety. The data, however, were sufficiently consistent to warrant the submission of averages for all dogs.

The averages on the five animals receiving 20 c.c. of aluminum cream 4 times daily for more than 4 months are shown in Table I. Similar data for Alucol are shown in Table I. The averaged acidity values of the non-medicated test meals before and after continued medication are shown as well as the medicated test meals before and after continued medication, and the four hour aspirations in which the meals had been medicated both before and after the continued period of medication. Such a scheme made it possible to determine the effect, if any, of long continued medication on the response of the stomach to non-medicated and medicated test meals. Any difference as much as ± 10% is significant.

It is obvious from an inspection of Table I that the administration of aluminum cream or Alucol in relatively large doses over a period of four months does not *decrease* the gastric secretory response to a test meal; no significant change occurred, the trend being toward a slight increase. In the case of Alucol and the plain test meals a definite increase occurred. This indicates that the stomach attempted to compensate for the buffering action of aluminum; and on the days that the non-medicated meal was given, the stomach continued to compensate as though aluminum had actually been added. This tendency to compensate is again shown in both the aluminum cream and Alucol data for the medicated aspirations, which were made 4 hours post-cibum, or at a time the stomach was practically free of food and medicament. As might be anticipated the acidity of the *medicated test meals* is reduced throughout the continued medication period, the reduction being greater for the first period of nine weeks than the latter seven weeks. This is not due to the stomach adapting itself to the aluminum after nine weeks or to the production of a gastritis, we believe, because when the average daily temperature meteorological curve is plotted alongside that of the gastric acidities, the decrease in acidities during the last seven weeks correlates with the average daily temperature, a fact that requires no discussion.

The attempt of the stomach to compensate for the effects of a neutralizing or buffering substance, of course, is a well-known phenomenon and occurs particularly in the case of alkalies (7). In the case of aluminum, however, the compensatory increase is not marked.

The effect of the addition of the aluminum preparations to a test meal. The same test meal employed in the former experiment was used and when medicated the same doses of the aluminum preparations given above were used. A gastric sample was obtained hourly for four hours.

Aluminum cream: Twenty-two animals were used. The non-medicated meal was fed 147 times and the medicated 137 times.

Alucol: The same experiment was conducted with Alucol on 28 animals. The non-medicated meal was fed 156 times and the medicated 117 times. The data are summarized in Table II.

First, it is to be noted that the data on the plain test meals in the two groups of animals (Table II) check remarkably, demonstrating the beauty of the averages of a large amount of data obtained under controlled conditions. The greater "buffering" effect obtained with Alucol in comparison to aluminum cream is due chiefly to the larger dose of Alucol administered, and we believe in part to the lower degree of solubility of Alucol. It is interesting that the ratio between the degree of lowering of free acidity at the 4 hour period in the case of aluminum cream and Alucol (0.028 : 0.038 = 74%) (Table II) is the same as the ratio between the "buffering" action of alumi-

TABLE II

Gastric acidities following test-meals (average values) expressed as per cent of HCl in 22 animals receiving Al cream

A	First Hour		Second Hour		Third Hour		Fourth Hour	
	Free	Total	Free	Total	Free	Total	Free	Total
Plain Test Meals	.018	.156	.044	.190	.087	.236	.125	.274
Medicated Test Meals	.014	.128	.034	.171	.073	.233	.097	.282
Reduction	.004	.028	.010	.019	.014	.003	.028	+.008
Per cent of reduction	22%	18%	23%	10%	16%	1%	22%	+3%

Gastric acidities following test meals (average values) expressed as per cent of HCl in 28 animals receiving Alucol

B	First Hour		Second Hour		Third Hour		Fourth Hour	
	Free	Total	Free	Total	Free	Total	Free	Total
Plain Test Meals	.017	.153	.045	.182	.082	.231	.113	.260
Medicated Test Meals	.009	.092	.027	.125	.055	.164	.073	.209
Reduction	.008	.061	.018	.057	.027	.067	.038	.051
Per cent of reduction	47%	48%	40%	31%	33%	29%	34%	20%

num cream and Alucol in the doses used at a 2 hour period (257.2 : 349.7 = 74%). This means that the differences observed are due chiefly to the differences in dosages of the two preparations.

Aspirations four hours after feeding, or at 1, 5, and 9 p.m. were made on both groups of animals, with and without the meals being medicated. In the aluminum cream group 82 "non-medicated" and 146 "medicated" daily aspiration tests were made; in the Alucol group 124 and 183, respectively. The animals did not receive more than 2 medicated sets of meals per week. These data because of their bulkiness will not be submitted. They agree essentially with the results shown under the fourth hour period in Table II. In fact, we made the aspirations to check the four hour data in Table II, and to observe if any accumulative effect of the aluminum might be observed to occur when given once or twice weekly at four hour periods during the day. A slight accumulative or compensatory effect was observed on the days the aluminum was given, which did not manifest itself when plain test meals were given.

HUMAN SUBJECTS

It is obvious that the ingestion of either of the two aluminum preparations will buffer gastric acid. However, we desired to perform a few experiments on several human subjects to ascertain how effective they might be.

Alcohol test meals: The normal gastric response of 6 graduate students, accustomed to the stomach tube, to 50 c.c. of 7% alcohol, after evacuating the gastric residuum, was determined. Then, the alcohol test was performed with Alucol (1.4 gm.) or Creamalin (4 c.c.), which was taken immediately after the alcohol. The curves (free acid only) of the average response of the group for two hours shows that the aluminum preparation reduced the free acidity for 45 minutes or longer. The variation in the response from subject to subject was rather marked, and the tendency to an increase in acidity after the aluminum had been evacuated, was characteristic of 4 of the 6 subjects.

Regular meals: The subjects (6 graduate students) in these experiments were instructed to choose a breakfast, a lunch and dinner and to ingest the same meals on three successive days, hourly samples of the gastric contents being withdrawn and titrated immediately. One day served as a control, and during the other two days either Alucol (1.4 gm.) or Creamalin (4 c.c.) were taken ½ hour after each meal and again at 10 a.m. and 3 and 8 p.m. The curves (free acid only) of the group averages show that the free acidity is reduced, but tends to rise to normal values an hour before the next meal. (It should be kept in mind that 4 c.c. of Creamalin and 1.4 gm. of Alucol buffer only about 40 c.c. of N/10 HCl in the test tube).

Similar experiments were performed in 10 subjects (students) except that the dose of the aluminum preparations was increased slightly and given hourly on the half hour for 14 hours. The subjects ate at 7 a.m., 12 noon, 6 p.m., and hourly at the half-hour they took 5 c.c. of aluminum cream (buffers 51.7 c.c. N/10 HCl in 1 hour and 46 c.c. in 0.5 hour) until 8:30 p.m. A gastric sample was removed on the hour and just before eating the noon and evening meal. A similar series of tests was made using 1.6 gm. of Alucol (buffers 52.6 c.c. N/10 HCl in 1 hour and 35.5 c.c. in 0.5 hour). Chart 1 shows the group averages and the results of subject Gr., whose free acid was reduced least of all. (The aluminum preparations tend to cause constipation in some normal subjects).

Effect of continuous and prolonged administration of aluminum hydroxide preparations on blood chlorides and plasma CO_2 combining power. The plasma CO_2 combining power and total blood chloride level were studied in eight dogs, four receiving 20 c.c. of aluminum cream and four 10 gm. of Alucol four times daily at 9 a.m., 1, 5, and 9 p.m. The plasma CO_2 combining power was found to be in the normal range for dogs, 46 and 56, average 49, volumes per cent. The blood chlorides expressed as sodium chloride ranged from 3.83 to 4.62, average 4.31 grams per liter which is slightly below or in the lower limits of the normal.

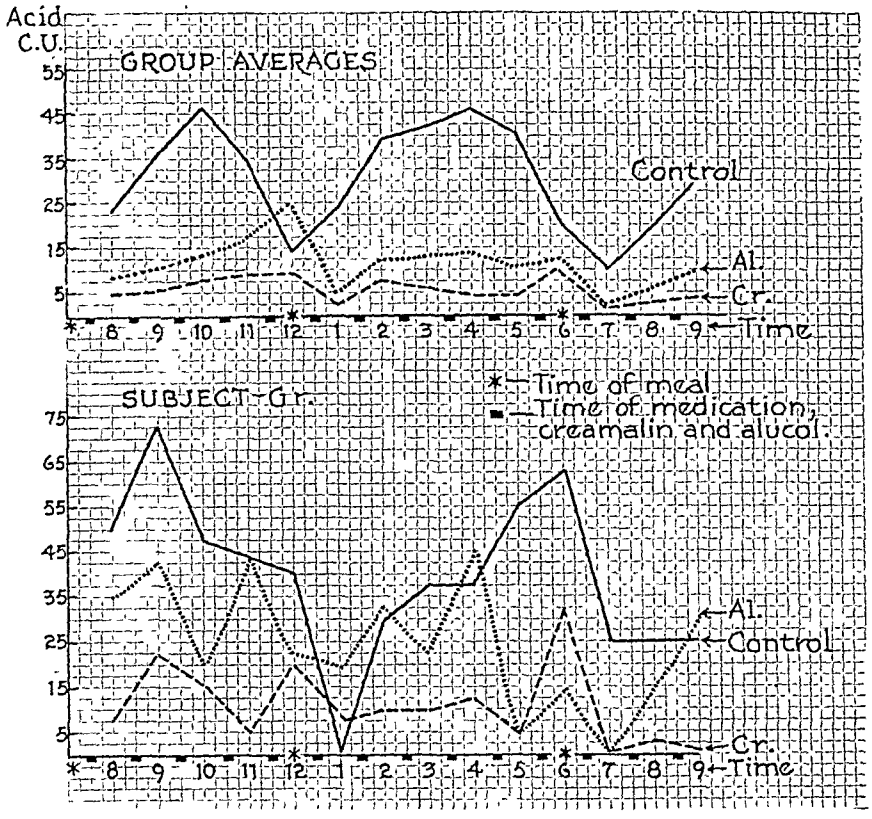


Chart 1

This confirms the findings of Einsel and others (2, 3) with the exception that our chloride values are somewhat lower, but our doses were relatively larger. The chloride values on patients receiving aluminum cream also fell in the lower limits of the normal range.

DISCUSSION

In view of the astringent action of aluminum hydroxide we rather anticipated a decrease in the gastric secretory response to a meal. No evidence showing that such occurs on the single or continued daily administration of the two preparations was obtained. The buffering action on the acidity of the gastric contents observed was of course to be expected and no significant difference in the two preparations in this regard was noted. It has been shown clearly by Boyd (7), using Pavlov pouch dogs, that alkalies such as sodium bicarbonate and calcium carbonate in ordinary doses given over a long period of time do not depress gastric secretion. Very large doses (3 gm. per kilo) depress, and on their withdrawal, a hypersecretion occurs. Small doses tend to augment secretion. No evidence was obtained indicating that the doses of the aluminum preparations used, given intermittently, stimulate secretion. However, the protracted administration of the preparations tended to augment secretion to non-medicated test meals given on days when medication was dithdrawn. This tendency of the stomach to compensate is analogous to that observed by Boyd in the case of alkalies, and in our experiment it cannot be ascribed to changes in acid base balance in the blood, since significant changes do not occur (2).

On the basis of our results pertaining to the amount of "buffering" of acid that occurred after the administration of the aluminum preparations, we doubt, as Einsel does, that the antacid properties of aluminum hydroxide preparations in the doses usually employed fully explain its reported effectiveness in "peptic" ulcer. In animals that have received the aluminum preparations for some time, one finds at autopsy the folds of mucosa in the stomach and duodenum covered with flaky curds, presumably precipitated mucin. Sometimes the duodenum is so coated that about two-thirds of its mucosa appears as if it had been covered with flour paste. This has been reported by numerous observers.

We chose the relatively large doses of the two aluminum preparations to administer to the dogs (a) because we doubted that one would desire to administer much larger daily doses to man, and never a larger per kilo dose, and (b) because we were interested in making observations on toxicity.

The question of the *toxicity of aluminum compounds* has been investigated and discussed pro and con at considerable length. The older literature has been reviewed by Smith (8). Unfortunately, much of the older work was not accompanied by histologic studies and the methods for the chemical analysis of tissue were not sufficiently sensitive and specific to render the results of value. Since 1929, however, more accurate methods (9-14a) for quantitating aluminum in biological materials have become available, the colorimetric method of Eveleth and Myers being the most suitable. It now appears established that rats may

be fed diets containing from 0.6 to 2.6 per cent aluminum chloride or other soluble aluminum salts for a year without producing histologic changes in their organs, affecting growth, producing anemia, or affecting reproduction (18-22). The only meager reports to the contrary (23) are incomplete. Aluminum compounds injected intravenously or subcutaneously in adequate doses are toxic, producing focal necrosis and swelling in the liver and kidney principally (11). So in the case of injection of aluminum, apart from the local irritating action of soluble aluminum compounds, the important question in regard to toxicity is how much aluminum is absorbed. Two studies (9a, 19) indicate that when soluble aluminum salts are perfused through an intestinal loop significant quantities are not absorbed, it being suggested that due to the alkaline reaction the colloidal hydroxide would be formed which one should hardly expect to be absorbed in appreciable quantities. When the more soluble compounds have been fed by mouth to rats and dogs in the amounts stated above, two investigations (13, 24) report no detectable absorption, four (14, 19, 11, 25) slight absorption, and two (23, 21) absorption in toxic amounts. As several investigators point out, the latter two investigations are open to criticism and could not be confirmed. Considering the results as a whole, it would appear that aluminum chloride, lactate and citrate, aluminum sulphate, when given in 2% per cent diets orally, results in a slight increase in the aluminum content of tissues. Only traces appear in the organs of the maximum normal are obtained. All results so far obtained indicate that chronic administration does not lead to a storage or a cumulative deposition of aluminum in the liver and kidney. Aluminum compounds of course are toxic (26). But, in rats placed on a diet to cause a nutritional anemia, aluminum was found to exert no effect (27), as in rats on a normal diet, conflicting results have been reported (2a, 18a). The German Bureau of Health (27a) fed dogs aluminum sulphate in quantities corresponding with 1 gm. of aluminum oxide (Al_2O_3) daily for a period of 8½ months. No change in the appetite or body weight occurred, and no harmful or change in the organs of the animals was observed. The aluminum content of the organs was within the normal range. A similar dose was given to man without causing symptoms. Traces of aluminum were present in the urine but a significant increase was not observed (12, 2 3a).

In our normal animals no significant changes in appetite and body weight have occurred with the relatively large doses of colloidal aluminum administered. However, we are interested in ascertaining the results of aluminum medication to Mann-Williamson dogs in which a tendency to hypersecretion of gastric juice exists along with a deficiency of alkaline pancreatic juice and bile to convert any aluminum chloride formed in the stomach to the insoluble hydroxide. To date our data for aluminum in the liver of such medicated dogs, receiving aluminum for from 3 to 8 months, have fallen in the normal range, except in one dog with a very fatty liver (aluminum, 0.14 mg. per gm. of dried liver). Underhill (11) found his highest hepatic content of aluminum in the liver of a man whose liver was fatty. Our complete data on this question will be reported when our results on Mann-Williamson dogs are completed.

CONCLUSIONS

1. When aluminum preparations (aluminum hydroxide cream and powdered colloid aluminum hydroxide powders in relatively large daily doses, larger than recommended in the therapy of "peptic" ulcer in man, are administered for a period of 4 months to normal dogs, a decrease in the gastric secretory response to a meal does not result. The decrease in acidity reported to occur in ulcer patients on aluminum therapy must be due to other factors than the effect of the aluminum directly on the gastric secretory mechanism. Under prolonged aluminum administration the gastric secretory mechanism tends to compensate for the buffering action of aluminum, or to respond to other possible effects of aluminum, since we observed slightly higher acid values for the gastric contents when non-medicated test meals were used. The failure to observe this effect in human patients (2) may be due to the smaller doses employed clinically.

2. When aluminum preparations are administered with a meal in a relatively large dose once or twice weekly, no definite change in the gastric secretory response to a meal is observed. Temporary "buffering" of acidity is of course obtained.

3. The health of the animals was not impaired, as judged by the outward appearances, in spite of the relatively large doses of aluminum. The aluminum content of the liver of seven of eight dogs receiving the aluminum for a period of from three to eight months was within the normal range of variation. A review of the literature pertaining to the question of the toxicity of aluminum compounds is presented.

4. The effects of administering aluminum preparations, both hourly and six times a day, on the free acidity of the gastric contents in normal human subjects eating three meals a day are reported. As might be anticipated, the aluminum preparations buffer free acid and are more effective in this regard when administered more frequently.

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Lymphosarcoma of the Stomach*

A Study of Four Cases

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ALTHOUGH sarcomata of the stomach comprise only about one per cent of all gastric neoplasms, a surprising number of cases is reported in the literature. In studying these reports, one is impressed with the difficulties which attended the clinical and roentgenological diagnosis of this condition and *also with the fact that an early diagnosis is even more* important in sarcoma than in carcinoma, at least from the standpoints of operability and curability.

Undoubtedly, the fact that sarcomata seldom involve the gastric mucosa early and therefore produce no characteristic deformity of the stomach on roentgen examination has led in many instances to the erroneous conclusion that no neoplasm was present, in spite of the clinical evidence. In such cases the possibility of sarcoma and its different pathological process from that found in carcinoma should be considered.

Our experience with a group of four proved cases of lymphosarcoma of the stomach will be discussed. Two of these, cases 1 and 4, have been reported previously (1, 2).

Case 1: A man, 55 years of age, complained of epigastric distress, characterized by a dull pain which came on immediately after eating. He had lost 20 pounds in weight. A roentgen examination made when his illness began (five months prior to admission) was reported as showing evidence of an ulcer on the lesser curvature of the stomach. The patient was given 24 daily intramuscular injections of a four per cent solution of l-hystidine monohydrochloride (Larostidin); this was followed by symptomatic relief for four months but the epigastric distress recurred, and another series of injections gave no relief.

The patient entered this Clinic and an abdominal examination revealed a large incisional hernia medial to the upper right rectus scar which followed previous cholecystectomy, but no palpable mass was present. Examinations of the blood gave normal findings. The night after his physical examination the patient had a gastric hemorrhage and entered the hospital. He was placed on strict ulcer management. Symptomatic relief lasted for two weeks but the epigastric discomfort returned and included night distress at 2 a. m. An Ewald meal at this time revealed an absence of free hydrochloric acid.

Roentgen examination was then made and the stomach would have appeared normal had there not been a careful study of the gastric rugae after the ingestion of a small amount of barium suspension. This procedure revealed an irregular ulceration on the posterior wall of the stomach, but it was not apparent when the stomach was completely distended with barium (Fig. 1). A diagnosis of an ulcerating neoplasm was made.

At operation, a large ulcerating lesion was found on the posterior wall of the pars media of the stomach; this process extended nearly to the cardiac orifice. The lesion was thought to be carcinomatous, and since no glandular involvement could be discovered a total gastrectomy was performed by Dr. T. E. Jones.

Examination of the stomach after removal revealed an indurated mass on the posterior wall just below the lesser curvature. On opening the stomach, a large indurated ulcer was found which measured 9 cm. longitudinally and 7.5 cm. transversely and extended from the cardiac opening toward the pylorus (Fig. 2). Microscopical examination showed it to be a diffusely infiltrating lymphosarcomatous growth involving all coats of the stomach (Fig. 3). Sections of three lymph nodes from the lesser omentum showed no evidence of metastasis.

Comment: This patient emphasizes (1) the necessity for a careful study of the rugae in all gastric roentgen examinations, and (2) the intermittent symptomatic relief which may occur in the presence of lymphosarcoma.

Case 2: This patient, a woman aged 55 years, entered this Clinic complaining of epigastric distress of a gnawing character. This was not relieved by food or soda and had been present for three weeks. Two weeks prior to entrance, she vomited a small amount of brownish material and the stools became dark in color.

Examination of the abdomen revealed a firm, rounded, smooth, and slightly tender mass, the size of a baseball, below the right costal border just inside the right mammary line. It moved with respiration and the liver could not be palpated.

Examination of the blood showed 3,010,000 red cells, 8,000 white cells, and 61 per cent hemoglobin. The blood Wassermann and Kahn reactions were negative. The Ewald test meal revealed an absence of free hydrochloric acid.

During the *roentgen examination*, the palpable mass was found to be outside the lumena of both the stomach and colon. It was movable and lay between the pyloric end of the stomach and the hepatic flexure of the colon, compressing both. The duodenum was not well visualized; by exclusion the mass was thought to be either in the duodenum or related thereto. The rugae in the pyloric third of the stomach were not well visualized but this was thought to be due to the extrinsic pressure of the mass (Fig. 4).

At operation, the mass was found to arise in the region of the pylorus of the stomach. Although the growth appeared to be extrinsic, it was considered an atypical variety of carcinoma, and partial gastric resection was done.

Excerpts from the *pathological report* are as follows: "The anterior surface of the stomach is smooth and glistening, but just proximal to the pyloric ring there is a bulging, smooth, regular protuberance, measuring 6 cm. in length and 4.5 cm. transversely. The posterior surface is roughened and irregular and has numerous fibrous adhesions over it. On opening the stomach, there is an ulcerated area which extends over the entire posterior wall and over the greater portion of the anterior wall, almost

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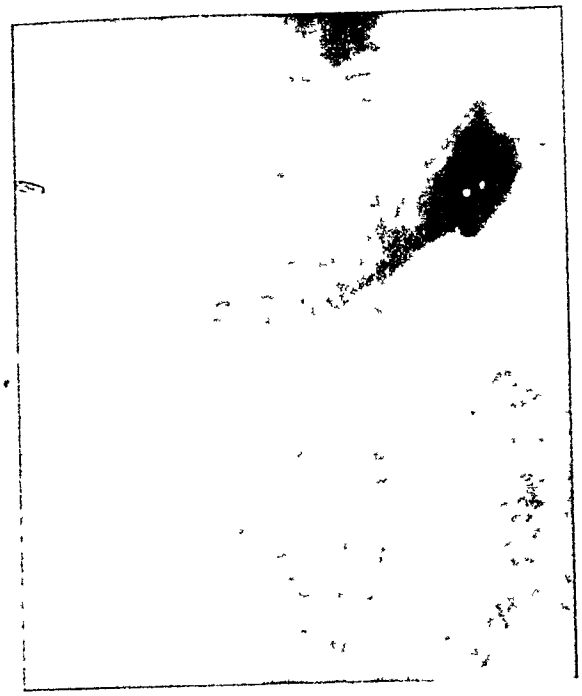


Fig. 1, Case 1. Roentgenogram showing evidence of an ulcerating neoplasm. When the stomach was completely filled with barium suspension, no evidence of abnormality was apparent.

completely encircling the stomach, except for a narrow strip on the lesser curvature" (Fig. 5). After microscopical examination, the pathological diagnosis was "lymphosarcoma, stomach and gastric lymph nodes" (Fig. 6).

The patient made an uneventful recovery from the operation and before leaving the hospital was given a course of deep roentgenotherapy to the upper abdomen and mediastinum. Later, metastases developed in the cervical lymph nodes and in the region of the right kidney. Roentgenotherapy was administered to both these areas, and even though there was a complete disappearance of all palpable nodes, death occurred seven months subsequent to operation.

Comment: In this patient, if the roentgenologist had interpreted his findings correctly the preoperative diagnosis should have been sarcoma. If more attention had been given to the gastric rugae and less attention to the feature of extrinsic pressure, the extensive shallow ulceration which nearly encircled the pyloric third of the stomach in association with an extra-lumenal mass would have been obvious.

Case 3: This patient, a man 68 years of age, complained of weakness and the loss of 37 pounds in weight during the preceding year. Approximately one year prior to entrance, he began to have indefinite pains in the abdomen, usually immediately after eating, and a diagnosis of "colitis" was made. He steadily grew weaker and lost weight but his abdominal distress subsided. Then a heavy feeling in the epigastrium developed. Six weeks prior to entrance, a roentgen examination was reported as showing no abnormality of the stomach.

Abdominal examination revealed no palpable organs or masses. Examination of the blood showed 2,640,000 red cells, 17,700 white cells and 45 per cent hemoglobin. Blood Wassermann and Kahn reactions were negative. The urine showed an occasional hyaline cast. The Ewald test meal revealed an absence of free hydrochloric acid. Examination of the stools was positive for blood.

Roentgen examination revealed an extensive neoplasm involving the proximal half of the stomach, particularly the lesser curvature where there was a large ulcer associated with evidence of considerable infiltration in the wall of the stomach.

The patient died thirteen days after admission. *At autopsy* the entire cardiac end of the stomach was made up of a pale, opaque, spongy, friable tumor. The tumor mass terminated about 5 cm. proximal to the pyloric sphincter on the lesser curvature. In the middle of the tumor area, there was a complete loss of gastric tissue, the tumor having extended into the liver, and the latter formed the anterior gastric wall in this area. Another ulcerated area in the cardiac end of the stomach was in continuity with the spleen.

The microscopical diagnosis was "lymphosarcoma of the stomach with extension into the left lobe of the liver, diaphragm, omentum, and mesentery, and metastases to the epicardium, mesenteric nodes, and ureter."

Comment: This patient illustrates extensive involvement of the mucosa late in the course of the disease. Apparently, the involvement occurred shortly before death because a roentgen examination was reported as showing no abnormality six weeks prior to entrance.

Case 4: A white boy, nine years of age, was admitted to St. Vincent's Charity Hospital in 1914, complaining of abdominal pain, nausea and vomiting which had been present for two months. His symptoms were those of an aching epigastric discomfort which began one year previously when he was struck in the "pit of the stomach" with a baseball.

Examination revealed emaciation and a tender tumor mass in the epigastrium. A clinical diagnosis of sarcoma of the stomach was made by Dr. F. E. Bunts and at operation, he found a large mass which involved the pyloric third of the stomach with glandular involvement of the greater curvature. A partial gastrectomy and a posterior gastro-enterostomy were performed in 1914. The patient made an uneventful operative recovery.

The surgical specimen weighed over 900 grams and a pathological diagnosis of lymphosarcoma of the stomach

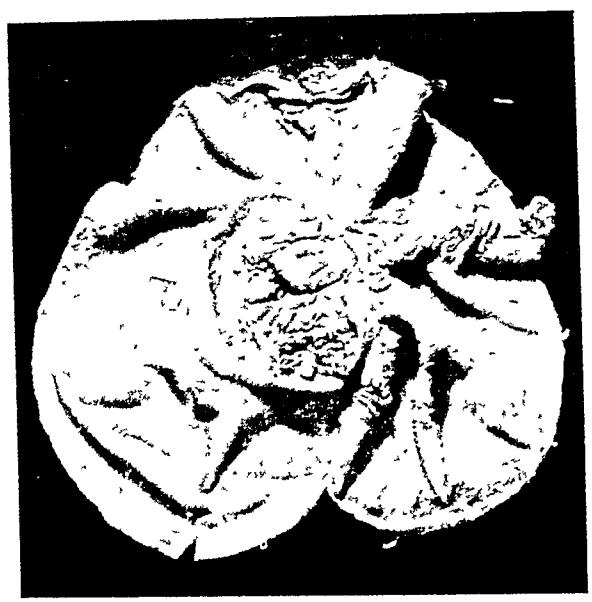


Fig. 2, Case 1. Photograph of gross specimen showing a large, indurated ulcer.

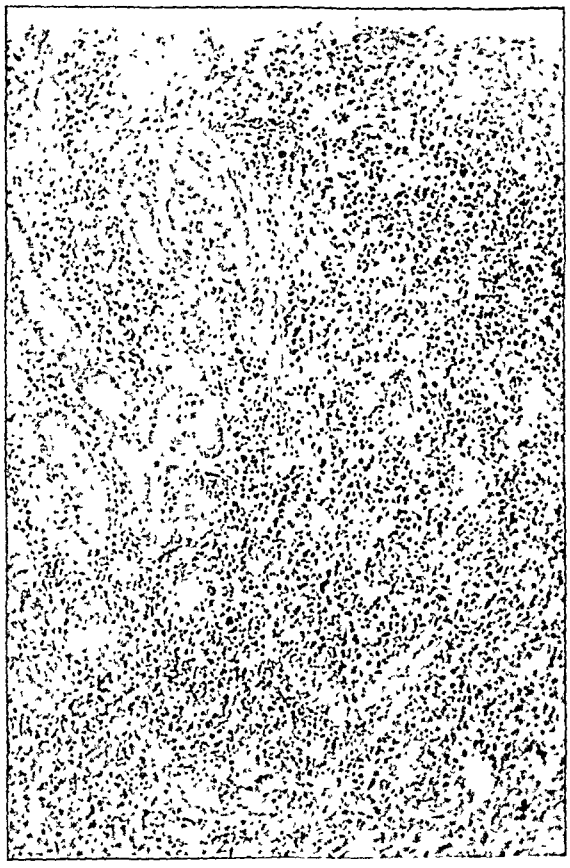


Fig. 3, Case 1. Photomicrograph showing a diffusely infiltrating lymphosarcoma (x 150).

was made. The patient is living and well today—twenty-two years after operation—with no evidence of recurrence.

INCIDENCE

Considerable interest in the subject of sarcoma of the stomach is evident from the amount of literature available. One of the most recent comprehensive reviews is that of Pack and McNeer (3) who cite the incidence as 1 per cent of malignant gastric tumors. In all cases of proven malignancy of the stomach at the Cleveland Clinic, the incidence of sarcoma is 0.7 per cent. The average age of our patients was 47 years, the youngest patient was 10 years of age and the oldest 68 years. It will be noted that this average age compares closely with that reported by other authors. The age incidence for sarcoma has been reported by some authors to be from five to twenty years below that of carcinoma, but Crohn (4) states that the greater number of cases occur in the fifth and sixth decades.

ETIOLOGY

The etiology of this, as of all malignant tumors, remains obscure. In Case 4 the patient dated the onset of his symptoms from the time he was struck in the "pit of the stomach" by a baseball. McWhorter (5) and others have pointed out that trauma may play a definite *rôle*. Kimpton (6), Warner (7), and Kapel (8) have reported cases in which the growth had existed for years and then underwent malignant change, and these writers feel that it is possible for a sarcoma to become engrafted upon a leiomyoma of the stomach just as such a process takes place in a leiomyoma of the uterus. Evidence has been presented to show that inflammation, irritation, preexisting neoplasms, chronic ulcers, and tuberculosis may be causative factors in the production of this type of tumor, but this has not been proved conclusively.

PATHOLOGICAL FEATURES

Gastric lymphosarcomata originate from the lymphoid follicles of the submucosa which form solid or cystic growths or a diffuse, infiltrating process. Finally they project either into the lumen of the stomach or outward under the peritoneum, more often the latter.

Most pathologists agree with Schlesinger (9) who classified sarcoma of the stomach into three types: First, the exogastric; second, the submucosal or possible intragastric; and third, the gross sarcomatous infiltrating type. The exogastric type, which arises in the subserous connective tissue layer, spreads between the layers of the gastrohepatic or gastrocolic omentum and may involve very little of the stomach wall. Unlike carcinoma, the line of demarcation between the tumor and normal stomach is usually well defined and sharply outlined. The other two varieties have the characteristics of lymphosarcoma as mentioned above.

Ewing (10) has divided sarcoma of the stomach into three distinct histological groups: the spindle cell myosarcomata, which usually constitute the exogastric type of growth; the lymphomatous tumors, which include the lymphosarcomata, and the miscellaneous

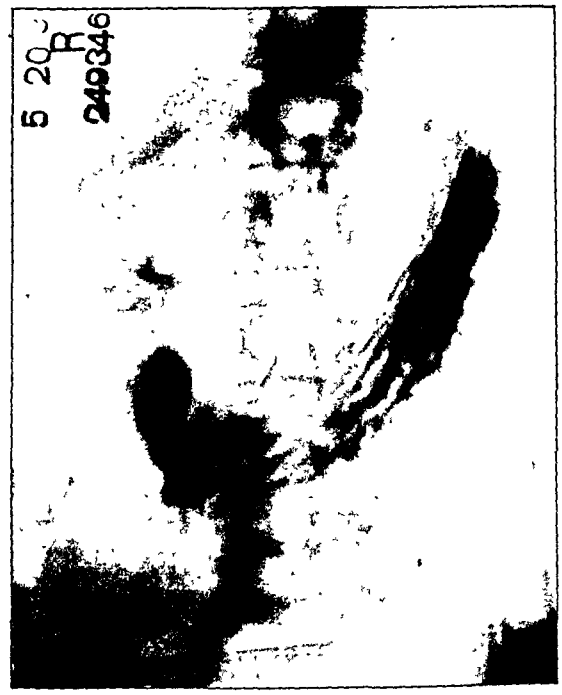


Fig. 4, Case 2. Roentgenogram of stomach made after the ingestion of a small amount of barium suspension. (I) Soft tissue mass in anterior wall of stomach (outside of gastric lumen). (II) The line of demarcation below which there was extensive ulceration almost completely encircling the pyloric third of the stomach.

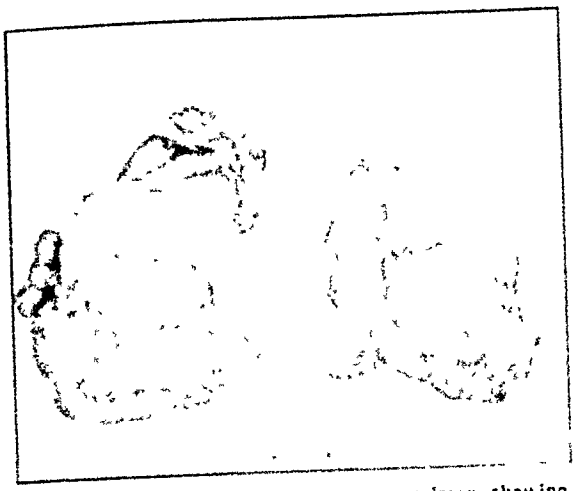


Fig. 5, Case 2. Photograph of gross specimen showing tumor in anterior wall of stomach and extensive shallow ulceration

round cell and alveolar types of sarcomata in which the structure does not appear to fall into any one of the common groups.

Unlike carcinoma, the mucous membrane in sarcoma is not involved until late in the course of the disease. When ulceration is present, it is usually due to a necrosis resulting from pressure or to the loss of blood supply rather than to neoplastic invasion. Thus, a large segment of mucous membrane may slough, leaving an extensive shallow ulcer as in Case 2. It appears probable that a sarcoma of the stomach may exist for months without involvement of the mucous membrane and finally an extensive slough may occur quite suddenly.

CLINICAL FEATURES

The exogastric variety of sarcoma, which usually produces a palpable mass, may be mistaken for retroperitoneal tumor, pancreatic or mesenteric cyst, and because splenomegaly is present in 10 per cent of cases of sarcoma of the stomach, Banti's disease also may be confused with this condition. In some of the reported cases of other varieties, the symptomatology was that of a benign peptic ulcer. Usually, soon or late the symptoms and signs of all sarcomata of the stomach are similar to those of carcinoma. In addition to epigastric distress, the patient generally complains of weakness and loss of weight. Secondary anemia and achlorhydria are common findings, as were present in three of our cases. Obstructive symptoms are rarely present because sarcoma is not prone to involve the orifices of the stomach.

The duration of symptoms may be longer than is the case in carcinoma. In a series of fifty-four cases reported by Balfour and McCann (11), the average duration of symptoms was more than a year; there was evidence of bleeding in sixteen and of a palpable tumor in over half the cases. In our patients, the average duration of symptoms was seven months, the shortest being three weeks and the longest one year.

ROENTGEN EXAMINATION

In view of the pathological features mentioned, the diagnostic reliability of the roentgen examination in sarcoma of the stomach cannot be so great as it is in other types of neoplasm or ulcerating processes which primarily involve the mucosa. The pathological process may be limited to the stomach wall without any involvement of the mucosa and there may be little if any disturbance in the peristaltic activity of the stomach. If a palpable mass is present, the roentgenologist may believe it has no connection with the stomach when there is no encroachment upon the gastric lumen (Case 2). On the other hand, there may be ulceration, the character and extent of which are entirely different from such usually encountered in other types of ulcerating process (Cases 2 and 3) (12). The routine mucosal relief methods of examining the gastric rugae are unusually important in sarcoma because the ulceration, if present, may be shallow (13). Cases have been reported wherein the gastric rugae were decidedly enlarged, suggesting a marked submucosal infiltration, but this finding alone makes impossible a differentiation between a hypertrophic gastritis, a submucosal infiltrating carcinoma, or an infiltrating lymphosarcoma (11). Too much emphasis cannot be placed on the fact that a roentgen examination may show no abnormality at one time but reexamination within a few weeks may show evidence of extensive ulceration (Case 3).

DIAGNOSIS

Strauss (15) and Haggard (16) have emphasized that the presence of hematemesis with melena in a young person and a palpable epigastric tumor without

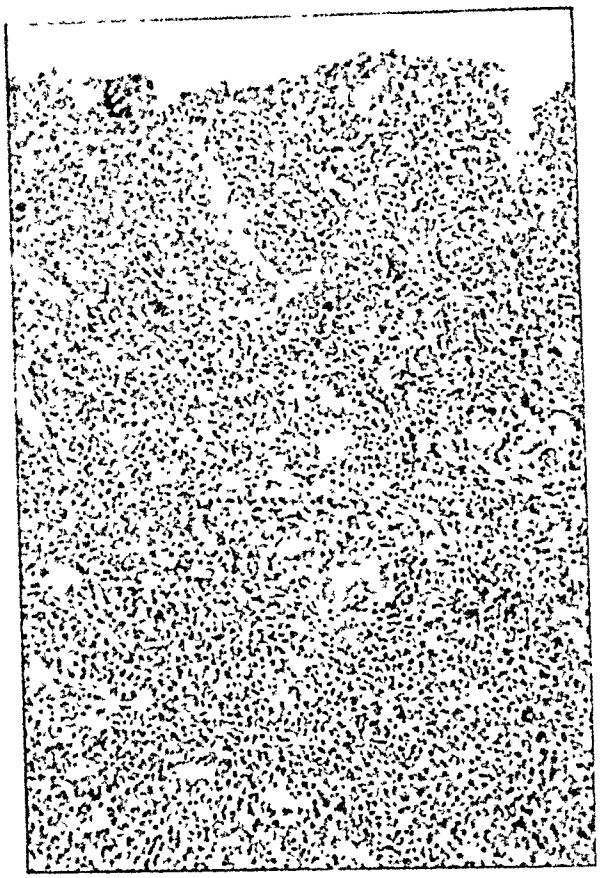


Fig. 6, Case 2. Photomicrograph showing lymphosarcomatous growth (x 150).

obstruction are suggestive of the presence of sarcoma of the stomach. A clinical diagnosis is seldom made preoperatively. However, we believe this lesion should be suspected in any patient, regardless of age, who has had continuous gastric symptoms and signs suggesting a neoplasm for a few months, a year or more, when the roentgenologist finds either no evidence of mucosal involvement or evidence of a large shallow ulceration which is not characteristic of either benign peptic ulcer or ulcerating carcinoma, especially if associated with an extralumenal mass. A sarcomatous mass which involves the lumen of the stomach obviously cannot be differentiated roentgenologically from other types of neoplasm. Renshaw (14) has recently reported a case of lymphoblastoma of the stomach with especial reference to the gastroscopic appearance.

TREATMENT

The operability of sarcomata of the stomach is greater than that of carcinomata. When the diagnosis *is established, resection of the growth is the procedure* of choice. Of the fifty-four cases in Balfour and McCann's series (11), thirty-eight were operable. At the time of their report, death had occurred in twenty-six. The average duration of life in those who died was eleven months and in those still living, it was five years.

If resection is not possible, palliative surgical measures may be employed. Pack and McNeer (3) state that all sarcomata of the stomach, except the spindle cell variety, are radiosensitive tumors. If the lesion is a lymphosarcoma, radiation therapy is especially indicated.

Pattison (17) has reported a case of diffuse lymphosarcomatous infiltration of the stomach on which a biopsy was made, and in which roentgenotherapy was the sole method of treatment. The patient was a boy of twenty years to whom repeated courses of deep roentgenotherapy were given. At the time of the report, fifteen months after the operation, the patient was in perfect health and had gained twenty pounds.

When there is roentgen evidence of neoplastic involvement of the cardiac end of the stomach and operation is not performed, the possibility of using a course of roentgenotherapy as a diagnostic procedure should be considered. If "progress" roentgen examinations show definite improvement, further roentgenotherapy would be indicated, conceivably on the basis of a radiosensitive sarcoma.

PROGNOSIS

The prognosis in sarcoma of the stomach, of course, varies with the character and duration of the lesion, the presence or absence of metastases, and whether or not it is operable or radiosensitive. It is unusual for these patients to survive for more than three to five years, because metastases are often present at the time of operation or initial roentgenotherapy. Earlier diagnoses may be made in the future. According to D'Aunoy and Zoeller (18), most authorities agree that the pedunculated growths, which usually are the spindle cell type, offer a better prognosis as compared with the infiltrating varieties which are most frequently lymphosarcoma or round cell in type. The reasons which they give are that those of the spindle cell type grow more slowly, have a tendency to remain circumscribed, do not metastasize so early, and are removable. However, in a review of the literature we have found that patients with lymphosarcoma comprise the greatest number of those surviving over a five-year period.

SUMMARY

1. The diagnostic difficulties encountered in four proven cases of lymphosarcoma of the stomach are reviewed.

2. The roentgen examination of the stomach may show no evidence of abnormality until late in the course of the disease inasmuch as the mucosa may not be involved prior to that time.

3. Two cases of lymphosarcoma are added to the literature.

4. In dealing with an obscure diagnostic problem involving the stomach, the rare possibility of sarcoma and its different pathological progress from that found in carcinoma should be considered.

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Intravenous Galactose Liver Function Test*

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IN a previous communication by one of us (1) the intravenous and oral galactose liver function tests were discussed. In the oral method there are at least two possible sources of error, which materially influence the sensitiveness of the test. The first is the intestinal rate of absorption. The second is a renal factor; the excretion of galactose may be influenced by a possible renal threshold value (2) or by renal disease. Both of these factors are eliminated in the intravenous test. On the other hand, the complicated chemical procedures and the multiple venipunctures constitute disadvantages and limitations to the practical applicability of the intravenous galactose liver function test. These, however, are of a degree comparable with other accepted tests like the glucose tolerance test and can be conducted by any well equipped clinical laboratory.

It is believed that galactose is metabolized by the liver only. Hence, any delay or diminution in the utilization of the galactose can be referred to a diminished liver function. A normal liver can metabolize within one hour, 25 gms. of intravenously injected galactose. Thus, any demonstrable galactose in the venous blood, one hour or longer after the injection of 25 gms. of galactose implies liver pathology. The rate of utilization can be studied by repeated observations at intervals of 15 minutes beginning one hour after the injection. The greater the retention of galactose, the greater the liver damage.

TECHNIQUE

Further observations with this test lead to some modifications of the technique. Instead of a 50 per cent, we are now using a 25 per cent solution of galactose. In this way, the viscosity of the solution is diminished and caramelization after autoclaving prevented. To avoid annoying reactions, characterized by chills and tremors, a buffer is added to the sterilized galactose solution. We have eliminated the analysis 30 minutes after galactose injection as of no practical value. On the other hand, a blood sample 75 minutes after the injection of the galactose solution proved of interest.

The present technique is as follows: A fasting venous blood sample is taken and oxalated in the usual way. Through the same needle 100 c.c. of a properly warmed, sterilized and buffered 25 per cent galactose solution, is injected slowly intravenously. Venous blood samples are taken and oxalated 60, 75 and 90 minutes later. The patient remains throughout this period in a fasting state.

From each of the four blood samples a Folin and Wu tungstic acid filtrate is prepared. The fermentable reducing substance is fermented out by the technique of Somogyi (3). The amount of non-fermentable reducing substance is determined by the method of Folin and Wu. The difference between the non-fermentable reducing substance in the first blood sample and in the blood samples following the injection of galactose, divided by 0.75 for the difference between glucose and galactose reduction, represents the galactose retained within the venous blood.

OBSERVATIONS

We have studied the rate of galactose utilization in five groups of patients: (1) Patients without demonstrable liver or biliary tract disease; (2) Patients with intrahepatic jaundice; (3) Patients with obstructive jaundice; (4) Patients with cirrhosis of the liver; (5) Patients with gall bladder disease.

(1) *The patients without liver or biliary tract disease* have all shown complete utilization within one hour of 25 gms. of intravenously injected galactose. Thus, the standard of normalcy has been established and our previous observations confirmed on a much larger group of cases. Included in this group are people without any demonstrable disease as well as patients with a great variety of pathological changes but without obvious liver pathology.

(2) *In patients with hepatitis*, whether toxic or infectious, retention of intravenously injected galactose one hour or longer is found in all cases except in subsiding catarrhal jaundice, when the galactose test may be negative. In a general way, the highest degree of galactose retention occurs at the height of the disease. The galactose retention drops rapidly as recovery from the liver damage ensues. There is no obvious relationship between the height of jaundice as determined by the icteric index or the Van den-Bergh test, and the degree of galactose retention. The latter diminishes or may become normal before the jaundice clears. The amount of galactose retention depends, on one hand, upon the amount of liver cell degeneration and, on the other hand, upon the amount of cell regeneration. Therefore, it varies from case to case and in the various stages of an individual case.

The curves of galactose retention in these cases vary a great deal. We have observed variations of 2.3 to 13.3 mgs. of galactose per 100 c.c. of blood plasma 60 minutes after the intravenous injection of galactose. Similar variations occur in the 75 and 90 minutes blood samples in which the galactose values varied from 0 to 10.1 and 0 to 2.6 mgs. per 100 c.c. of blood plasma respectively. The mean curve of 10 cases studied is shown on Chart I.

(3) Six *cases of obstructive jaundice* were studied with the intravenous galactose liver function test. Four of these cases had a carcinoma of the head of the pancreas and two a common bile duct stone. Two cases of carcinoma of the head of the pancreas and one case of common duct stone with obstruction gave

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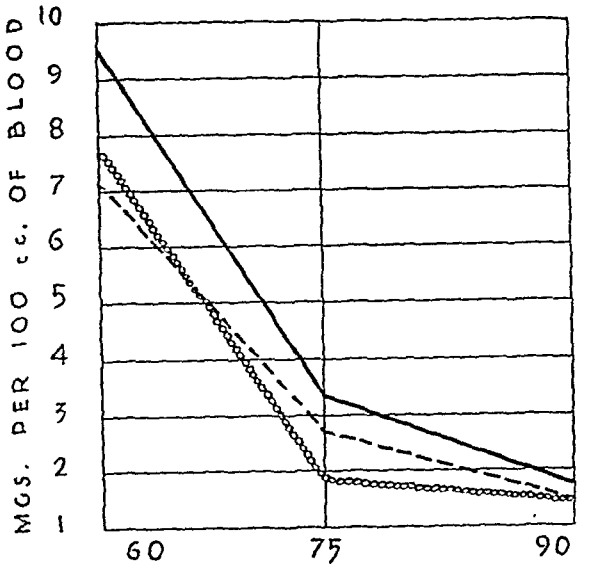


Chart I

Minutes after injection.
——— curve in cirrhosis of liver ..... curve in hepatitis
oooooo curve in obstructive jaundice.

positive galactose tests. Thus, 50 per cent of the obstructive jaundice cases had some galactose retention one hour after an intravenous injection of the standard amount of galactose. The mean curve in the three cases is shown on Chart I. It can be seen from the chart that the greatest variation between the two types of jaundice occurs at 75 minutes. In obstructive jaundice there are only traces (0.70 mgs. per 100 c.c.) while in intra-hepatic jaundice 2.7 mgs. is found in the blood plasma. Both at 60 and 90 minutes the galactose retention in both groups is practically the same. It would appear that the factor, which determines whether galactose is retained or not, is the duration of the obstruction and not the degree of jaundice. In the cases with a positive test the jaundice was distinctly of longer duration than in the negative ones. This should be interpreted as a secondary hepatitis or biliary cirrhosis from a long-standing obstruction.

(4) Twenty-five cases of *portal cirrhosis* were studied with the intravenous galactose liver function test. In this group 16 patients (64 per cent) gave a positive, while 9 (36 per cent) gave a negative test. The mean curve of the 16 positive cases is shown in Chart I. The galactose values were as follows: At the end of one hour (9.42 mgs. per 100 c.c.) at 75 minutes (3.33 mgs. per 100 c.c.) and at 90 minutes (0.96 mgs. per 100 c.c.). The degree of retention is higher than in the two previous groups. In individual cases the amount of galactose in the venous blood varied at 60 minutes from 2.7 to 22.4 mgs., at 75 minutes from 0 to 13.3 mgs. and at 90 minutes from 0 to 10.4 mgs. As these figures show, there is a great deal of variation in these cases. We were, however, unable to correlate the retained galactose with jaundice or size of the liver. In all cases of portal cirrhosis with ascites galactose retention was present.

(5) All cases of *cholecystitis*, with or without stones in the absence of obstruction to the biliary tract, metabolized 25 gms. of intravenously injected galactose within one hour. Several cases had a mild transient jaundice. As has been mentioned before, one of the two cases of cholelithiasis with common duct obstruction gave a positive intravenous galactose liver function test.

DISCUSSION

Positive intravenous galactose tests indicate liver damage. On the other hand, negative tests do not rule out liver disease. At no time did we find galactose retention at the end of an hour in patients without demonstrable liver or bile duct disease. Gall bladder disease without common bile duct obstruction gives a negative intravenous galactose liver function test. Intrahepatic jaundice cases show a definite retention of galactose which is demonstrable in all cases, except in the stage of recovery. In obstructive jaundice, retention of galactose may be absent or present. If present, the amount of galactose retention seems to depend upon the duration of biliary obstruction. Therefore, if this test is to be used in the differential diagnosis between intrahepatic and obstructive jaundice, it must be performed in the early stages of the disease. When so done, a positive test indicates intrahepatic jaundice. When the disease is of long standing, intrahepatic jaundice may give a negative response, while obstructive cases show a tendency to galactose retention. Apparently, the higher the amount of retained galactose the greater the liver damage. With a diminishing amount of galactose within the blood on repeated examinations a conclusion of improved liver function is justified. It will bear reemphasizing that the galactose test does not parallel the degree of jaundice. Very frequently in intrahepatic jaundice the galactose liver function test becomes negative before the jaundice clears. Therein lies its importance from a prognostic point of view. Whereas by the oral method in the absence of jaundice the galactose test is of no value, by the intravenous test indications of liver damage may be obtained.

The highest degrees of galactose retention are encountered in portal cirrhosis of the liver. The test is positive in 64 per cent of cases. In 36 per cent it is negative whether jaundice is present or not. We have not encountered, however, cases of cirrhosis of the liver with ascites which gave a negative intravenous galactose liver function test. Cases of cardiac ascites give persistently a negative galactose test. Therefore, this test can be used in the differential diagnosis of the etiology of ascites.

SUMMARY

The intravenous galactose liver function test, the technique of which is here described, is positive in a high per cent of cases with liver damage. It is negative in all cases where there is no liver damage. A negative test, however, does not rule out liver disease. In the early stages of jaundice it may be used in the differential diagnosis between hepatic and obstructive jaundice. In ascites it is of help in differentiating between a cirrhosis of the liver and cardiac decompensation. The progress of hepatic disease may be followed by repeated intravenous galactose liver function tests.

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Gastro-Intestinal Symptoms of Pelvic Origin*

By

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GASTRO-INTESTINAL symptoms may arise from lesions outside of the alimentary tract. They may arise from causes within the pelvis.

The "stomach" has been called the "spokesman" of the body. But the abdominal spokesman simply tells of trouble. It remains for the physician to identify the organ or diseased tissues causing the symptoms.

The pathologic background for gastro-intestinal symptomatology is quite diverse and includes lesions in the head, thorax, abdomen, and extremities. In fact there is hardly an organ in the body that does not cause digestive symptoms directly or indirectly at one time or another. This discussion is being confined to the pelvic causes of gastro-intestinal symptoms.

The literature on the pelvic origin of gastro-intestinal symptoms is rather scant.

Walschied has pointed out that in the causation of gastro-intestinal symptoms by pelvic lesions, the following factors operate: a reflex mechanism through the sympathetic and parasympathetic nervous system, the influence of hormones and mechanical compression of the lower bowel.

Moldavskaya-Svet reports a series of 169 patients who had both gastro-intestinal symptoms and gynecologic disease, in many of whom it was difficult to determine the primary syndrome. He divides the gastro-intestinal syndromes of these patients in three groups, (1) those who manifested disturbances in the motor function of the intestine as constipation or diarrhea, (2) those who manifested some inflammatory process of the large bowel or the appendix, and (3) those who manifested the peptic ulcer syndrome.

PATHOGENESIS

An analysis of the mechanism of the interrelationship of gastro-intestinal and pelvic disease shows that there are four relationships that come into consideration: (1) the anatomic, (2) the neurologic, (3) the chemical, and (4) the extraneous and accidental factors.

Mechanism of the interrelationship of gastro-intestinal and pelvic disease.

1. Anatomic Relationship,
    1. Contiguity,
    2. Ligaments,
    3. Peritoneum continuity,
    4. Peritoneal folds.
2. Neurologic Relationship,
    1. Sympathetic nerves,
    2. Parasympathetic nerves,
3. Chemical Relationship,
    1. Endocrines,
    2. Humoral factors,
4. Extraneous and Accidental Factors,
    1. Pregnancy,
    2. Tumors,
    3. Inflammations,
    4. Malignancies,
    5. Adhesions,
    6. Malpositions,
        (a) Retroversions,
        (b) Etc.
    7. Sinuses and Fistulas,
    8. Hypertrophies,
    9. Dilatations,
    10. Foreign Bodies,
    11. Fecal Impaction,
    12. Various, unusual.

1. *Anatomically* there is a close propinquity between the pelvic reproductive organs and parts of the digestive apparatus. Thus, there is a direct contiguity between the prostate or the uterus, the Fallopian tubes and the ovaries and those loops of the small intestine which descend into the pelvis as well as the pelvic colon which normally descends through the pelvic basin to lie posteriorly to the uterus or the prostate. In some individuals, the caecum and appendix occupy a low position and lie within the pelvic basin instead of being in the usual McBurney's area. This is especially true of persons of the asthenic *habitus*. In these individuals, the appendix, the right tube and the right ovary are contiguous. Inflammations of one organ readily involves the neighboring organs by the simple process of direct extension. In such individuals, salpingitis may give rise to a secondary appendicitis or *vice versa*. The clinical picture becomes very obscure as to the sequence of pathologic events. The differential diagnosis becomes difficult to make, indeed if it can be made at all. The writer has observed at the operating table on numerous occasions the appendix and right adnexa matted together into a fibrin covered mass. In these patients, all the pathology is available to direct inspection, nevertheless it is a matter of conjecture as to the order of pathologic events. Small wonder, then, that it is difficult at times to make a pre-exploratory differential diagnosis between salpingitis and appendicitis.

2. *Neurologically*, both the pelvic organs and approximately the distal half of the colon including the rectum are interrelated. Both systems derive their nerve supply from the same sources. Both are largely supplied by the parasympathetic pelvic nerves which are spinal nerves, and the sympathetic nerves derived from the inferior mesenteric plexus.

Visceral neurology according to Livingston, offers a means for satisfactorily interpreting and unifying a considerable number of seemingly isolated clinical observations.

Those organs which are innervated by spinal nerves of similar spinal levels are regarded as being of

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TABLE I

Summary of case reports

Case	Age	Symptoms				Pathologic Lesion	Surgical Treatment	Results
		Duration	Gastro-intestinal	Constitutional.	Pelvic			
(1) Mrs. A. P. R.	39	5 yrs.	Flatulence, constipation alternating with diarrhea, mucus in stool, cramps, abdominal pain.	Palpitation, dizziness.	Slight dysmenorrhea.	Uterine fibroid.	Hysterectomy.	Greatly improved.
(2) Miss M. R.	32	3 mo.	Diffuse abdominal pain, R.L.Q. pain, flatulence, diarrhea alternating with constipation.	Underweight 20 lbs.	None.	Right ovarian cyst.	Right oophorectomy, prophylactic appendectomy.	Greatly improved.
(3) Mrs. G. S.	40	8 yrs.	Flatulence, constipation, abdominal distress.	Secondary anemia.	Slight, dysmenorrhea.	Fibroid uterus.	Hysterectomy.	Greatly improved.
(4) Mrs. M. C.	64	10 yrs.	Flatulence, constipation, abdominal distress.	Hot flushes, nervousness, fatigue.	Amenorrhea.	Calcified pelvic tumor.	Refused.	Unimproved.
(5) Mrs. A. L.	32	4 yrs.	Flatulence, biliousness, distress after eating, abdominal distress, epigastric fulness.	Underweight 14 lbs.	None.	Fibroid uterus.	Tumor excision.	Greatly improved.
(6) Mrs. J. S.	49	12 yrs.	Abnominal pain, cramps, nausea and vomiting, loss appetite.	Nervousness.	None.	Pelvic tumor.	Refused.	Unimproved.
(7) Mrs. L. F.	25	6 mo.	Nausea, epigastric distress, flatulence, pain in R.L.Q., peristaltic unrest, constipation.	Headache, palpitation.	None.	Chocolate cyst of right ovary.	Right oophorectomy.	Greatly improved.
(8) Mrs. S. G.	37	3 yrs.	Pain in R.L.Q., abdominal distress, diarrhea alternating with constipation, flatulence.	Urticaria, secondary anemia.	Leucorrhea, dysmenorrhea, polyuria, dysuria.	Bilateral pyosalpinx.	Bilateral salpingectomy.	Greatly improved.
(9) Miss J. B.	26	3 yrs.	Diarrhea alternating with constipation, flatulence.	Dizziness, short of breath.	Backache.	Bilateral ovarian teratoma.	Bilateral oophorectomy.	Greatly improved.
(10) Mrs. K. T.	45	10 yrs.	Indigestion, diarrhea alternating with constipation, loss of appetite, mucus stools.	Secondary anemia, underweight 20 lbs.	None.	Fibroid uterus.	Hysterectomy.	Greatly improved.
(11) Miss D. J.	50	7 yrs.	Diarrhea alternating with constipation, flatulence.	Secondary anemia, underweight 15 lbs.	Amenorrhea.	Fibroid uterus.	Hysterectomy.	Greatly improved.
(12) Mrs. J. E. H.	26	2 yrs.	Flatulence, constipation alternating with diarrhea, abdominal consciousness, mucus stools achylia.	Underweight 25 lbs.	None.	Marked retroversion.	Suspension of uterus.	Marked improvement.

embryonic, segmental relationship. Nowhere in the body is this metameric relationship better illustrated than here. The pelvic reproductive organs and the distal colon are all innervated by the pelvic nerves which originate at the second, third and sometimes the fourth sacral levels.

Sympathetic reflexes tend to follow their embryonic segmentation areas, that is, they tend to be segmental or metameric in expression. This tendency may result in the spreading of the afferent impulses to the other organs of the same spinal level, with resulting overlapping of symptoms from one system to the other.

3. *Chemically*, there is evidence pointing to the influence of the reproductive system and endocrine glands upon the gastro-intestinal tract. Thus, Artz observes that pregnancy apparently influences the gastric physiology. He reports that the free and total

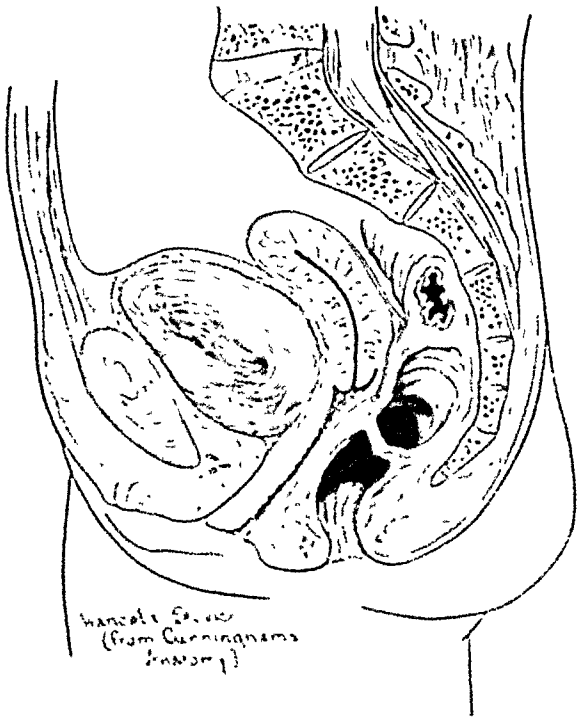


Fig. 1. Mesial section of the pelvis in an adult female showing the anatomic relationship of the reproductive system to the pelvic colon.

acidity of the stomach are lower in the pregnant than in the nonpregnant woman. Nakai likewise reported that the acidity of the stomach is lower in the pregnant woman especially during the first five months of gestation. As early as 1905, Kehrer surveyed the same relationship. In 1931, Macon of Denver, likewise made similar observations.

Strauss and Castle reported upon 21 pregnant women in whom they made 142 gastric analysis during gestation and in the puerperium. They record that 75% of the women did not secrete normal amounts of free hydrochloric acid during more than half the period of pregnancy; whereas the large majority of such patients secreted higher concentrations of hydrochloric acid after delivery; then the acid secretion of the stomach was found to be approximately three times as great as in the sixth month of gestation.

In dogs, in which the ovaries have been removed, Badylkes observed a reduction in the secretion period of the gastric juice, whereas injection of ovarian substance prolonged it. Hess and Faltitscheck believe that in menstruation the equilibrium of the vegetative nervous system is altered; this may result in hyperirritability of the parasympathetic nerves and may manifest itself in exaggerated motility and secretion of the stomach.

Klein reports an unusually interesting experiment from which he seems to have demonstrated the "humoral" influence of the reproductive system upon the digestive tract. He studied the effects of lactation on the acid secretion of transplanted gastric pouches in dogs. He made a series of such transplanted pouches into the subcutaneous tissue of the abdominal wall in dogs. These pouches had been completely separated from the old blood and nerve supply. Klein then observed that the concentration and quantity of hydrochloric acid were increased during lactation. In those animals where there had been no secretion prior to lactation, it first appeared during this period. Klein believes that the causative factor for the increased secretion at least is partly explained on a humoral basis, inasmuch as, in one dog, the transplanted pouch consisted only of mucous membrane and submucosa completely severed from the stomach and thus the vagus, the sympathetic, the gastric blood vessels, as well as the myenteric plexus were eliminated.

4. *The fourth group* is composed of the extraneous and "accidental" factors. The most important of these is pregnancy. Next to pregnancy are tumors which originate in one of the systems and which then impose their influence on the adjacent viscera by reason of the natural growth of their sphere of influence. Since tumors of the reproductive organs are of greater frequency than tumors of the lower bowel, pelvic tumors of the reproductive system occupy a special place of importance in this discussion.

Any abnormal growth in the pelvis will influence contiguous organs. At first this influence causes an irritation of the affected organ. If the irritation persists, it may develop into an inflammatory reaction.

A glance at any standard text book on anatomy giving a mesial section of the pelvis shows the close relationship of the uterus to the pelvic colon. It becomes evident that any appreciable enlargement of the uterus, irrespective of whether it is due to pregnancy, inflammation, tumor or other causes, cannot fail to press upon the colon. Pressure on the colon may result in an obstruction of its lumen and thus

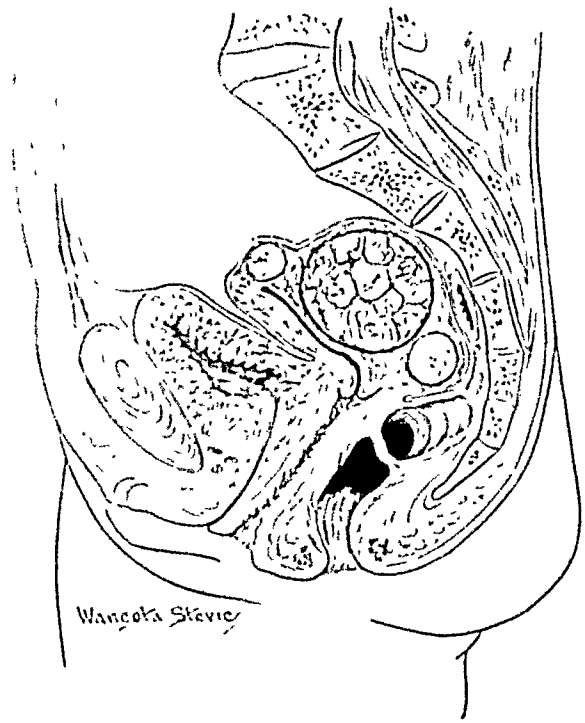


Fig. 2. Mesial section of the pelvis in an adult female showing a tumor of the uterus and its influence on the digestive apparatus resulting in compression and distortion of the pelvic colon.



Fig. 3. Roentgenogram showing a calcified pelvic tumor in patient M.C., whose presenting complaint was a digestive syndrome.

interfere with the normal movements of the intestinal content thereby causing constipation or the "colon irritation" syndrome.

In the experience of the writer, the majority of instances of gastro-intestinal symptoms due to pelvic origin, other than pregnancy, resulted from tumors.

Additional causes of gastro-intestinal irritation arising from the pelvic reproductive organs are: malpositions of the uterus, inflammations, sinuses, fistulas, adhesions, benign or malignant tumors of the ovaries, the tubes or the prostate gland.

Inflammations, hypertrophies and tumors of the prostate can disturb the gastro-intestinal tract in the same manner that corresponding disease in the female affects it Goldstein calls attention to the fact that nausea, vomiting, loss of weight, and other gastro-intestinal symptoms may indicate disease of the prostate gland.

Not all pelvic tumors necessarily disturb the digestive tract The tumor must be so located that it exerts pressure on the pelvic colon or rectum or otherwise involves them. A large cyst of the ovary may exert no deleterious effect by reason of its lack of contact with the gastro-intestinal tract. The same applies to numerous other conditions arising within the pelvis.

SYMPTOMATOLOGY

There are no pathognomonic gastro-intestinal signs or symptoms which suggest the presence of pelvic pathology. The digestive disturbances that arise are no different than those caused by a dozen different etiologic factors.

The commonest clinical syndrome is the nausea and vomiting of pregnancy. This syndrome is so general that it is usually accepted as part of the clinical manifestation of pregnancy. In fact, most text books on obstetrics list "morning sickness" as one of the presumptive signs of pregnancy. Above, we have pointed out that certain stages of pregnancy influence the gastric physiology by reducing the acid secretion.

Next in frequency to the "morning sickness" of pregnancy, is the result of pressure from pelvic tumors. This usually manifests itself in the syndrome of "irritable colon," thereby giving rise to spastic constipation, unsatisfactory stools, small caliber passages, rectal spasm, abdominal consciousness, abdominal pain, flatulence, epigastric distress. Later, the patient may develop diarrhea, mucus stools, diarrhea alternating with constipation, or mucous colitis. The cathartic and enema habit follow logically; still later, the constitutional symptoms of irritable colon develop, as chronic fatigue, insomnia, secondary anemia, introspection, etc.

We have not encountered any patients who presented the peptic ulcer syndrome as reported by Moldavshaya-Svet, although several of our patients did complain of epigastric pain, hyperacidity, and heartburn. However, we considered these to be reflex symptoms from colon irritability; such were especially noted when the X-ray showed marked spasticity of the colon but the stomach was found to be within normal limits.

The following *Case report* shows a typical instance of irritable colon caused by pelvic tumor.

Mrs. A. P. R., age 39, complained of bowel trouble of five years' duration. She stated that her stools were no longer satisfactory or normal, as they had been previously. She was constantly constipated except at times when she would experience attacks of diarrhea lasting one or two days. The stools were of small caliber, unsatisfactory and contained mucus. She had abdominal cramps and was "abdominally conscious" most of the time. She felt tired, fatigued readily, had attacks of palpitation and dizziness, and was introspective. She had no pelvic complaint but in response to questioning admitted a slight dysmenorrhea.

Physical examination: An anemic appearing woman not acutely ill; she weighed 130 pounds, was 5 feet, 7 inches in height; her pulse was 90; temperature 97.4; respiration 14; blood pressure 110/70; no lesion of heart and lungs; abdomen exhibited a spastic, palpable, and tender colon; liver and spleen not palpable; pelvic examination: a definite fibroid the size of an orange on the posterior uterine segment; it pressed on the rectum. The X-ray examination demonstrated a spastic colon throughout its entire length, associated with delayed emptying time. Blood examination revealed moderate secondary anemia. The stool contained mucus. The basal metabolic rate and urine were normal. *Diagnosis:* spastic colon, mucous colitis, fibroid of the uterus, secondary anemia.

Medical management was prescribed. This included a bland diet, intestinal lubrication, sedative therapy, and an autogenous vaccine made from the predominating stool organism. The result was unsatisfactory. A year later the patient continued unimproved, so a hysterectomy was performed. Following such, she improved and was well in a reasonable time. She remained well.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis between primary gastro-intestinal and digestive symptoms from pelvic disease is possible only by thorough, general, physical and special system examination. Only the poorly trained physician or the "inclusive" specialist fails to examine patients physically, from all angles. Particularly is his physical examination guided by the taking of a history which is, in all ways, comprehensive. Apart from history and thorough physical examination (including rectal and vaginal exploration) all possible laboratory aids, including competent X-ray studies, are requisites if one is to avoid pitfalls, diagnostically

and therapeutically. Patient No. 4 here reported, at X-ray examination, was found to have a calcified, pelvic mass; advantage, likewise, should be taken of injecting the uterus and the tubes by substances opaque to the X-ray, when digital examination suggests pathology.

A careful inquiry into the pelvic history of each patient frequently will disclose anomalies of the menstrual cycle, dysmenorrhea, metrorrhagia, amenorrhea, dysuria, polyuria, painful coitus, etc.; the pelvic examination usually will demonstrate pathology or visceral malpositions. The writer frankly confesses that it is not an uncommon experience in his practice to have the pelvic examination reveal a pelvic mass in patients in whom it was not suspected previously and where the history predominantly was that of dyspepsia or alimentary tract irritability. In the diagnosis of digestive complaints, one must be *suspicious* of disability in systems apart from the gastro-intestinal tract, before condemning it to harboring primary pathology. Eternal vigilence is the price of diagnostic accuracy.

TREATMENT

The first principle is to remove the cause. Fortunately, in many patients, this can be done satisfactorily by combined medical and surgical procedures. Benign tumors can be removed, malignant tumors treated according to indications, malposition of viscera, such as retroversion, can be corrected, inflammations appropriately managed as findings warrant. In those dyspeptic patients where the essential anomalies lies in pelvic lesions, the removal or alleviation of such disturbances, commonly is followed by digestive tranquility.

Primary gastro-intestinal disease may coexist in a patient who has pelvic disease particularly in patients of middle age. Thus, a patient with acute salpingitis also can harbor a peptic ulcer, gall stones or true colitis. Hence, even should pelvic examinations disclose pathology which may be assumed to account for dyspeptic upsets, one never should be willing to allow his final diagnosis to so rest until by all available, modern means, he has excluded actual disease in the alimentary tract and its associated organs.

CASE REPORTS

We are reporting in tabular form for purpose of brevity, a series of twelve patients other than those of pregnancy, with typical gastro-intestinal syndromes which were caused by pelvic pathology. These disturbances occurred in women whose *ages* ranged from 26 to 61. The *symptoms* were experienced for from 6 months to 12 years. The *gastro-intestinal symptoms* generally encountered in the irritable colon group were: constipation, unsatisfactory stools, small caliber stools, mucus stools, flatulence, rectal spasm, peristaltic unrest, constipation alternating with diarrhea, "abdominal consciousness," epigastric distress, heartburn.

The *constitutional symptoms* encountered were: palpitation, dizziness, underweight, secondary anemia, "hot flashes," fatigability, nervousness, headache, urticaria, dyspnoea. The *pelvic symptoms* experienced were leukorrhea, dysmenorrhea, backache, amenorrhea, dysuria, polyuria.

The pelvic lesions found were: fibroid tumor of the uterus in five, unilateral ovarian in two, bilateral teratoma of the ovaries in one instance, bilateral pyosalpinx in one, an undetermined calcified pelvic tumor in one patient, a pelvic tumor of undetermined nature in one patient and a marked uterine retroversion in one patient.

In all of these patients, symptomatic treatment for the gastro-intestinal syndrome was tried, but the results were unsatisfactory. Surgical treatment of the pelvic lesion was advised in all cases. Ten patients submitted to surgery and greatly improved. Two patients refused surgery and remained unimproved. In the group that was operated upon, relief of the gastro-intestinal symptoms seemed to be due to the eradication of the pelvic pathology or to corrections of anomalies. This series is small but we believe that its citation will emphasize sufficiently the necessity for considering seriously the possibilities of pelvic pathology, particularly in women, who are exhibiting dyspepsia—often not "true to type" for definite organic disease of the digestive system

SUMMARY

1. Gastro-intestinal symptoms may arise from lesions outside of the gastro-intestinal tract.

2. They may arise from causes within the pelvis.

3. An analysis of the mechanism of the interrelationship of gastro-intestinal and pelvic disease shows that there are four possible relationships that come into consideration, namely the anatomic, the neurologic, the chemical, and the extraneous and accidental factors.

4. Pregnancy constitutes the etiologic factor of greatest importance within the pelvis which causes digestive symptoms. Next in importance are pelvic tumors which impose their influence on the adjacent bowel.

5. There are no gastro-intestinal symptoms pathognomonic of pelvic origin.

6. The common gastro-intestinal syndromes of pelvic origin are, first, the morning sickness of pregnancy, and second, the colon irritation syndrome caused by pelvic tumors, but any digestive symptom may be encountered.

7. The diagnosis of pelvic lesions causing gastro-intestinal symptoms is usually arrived at from a consideration of the pelvic history and thorough general as well as pelvic examination.

8. A pelvic as well as a rectal examination constitute an integral part of every well conducted gastro-intestinal examination.

9. A series of twelve patients illustrating typical examples of gastro-intestinal complaints due to pelvic disease is reported.

10. Symptomatic medical treatment for the gastro-intestinal complaints was unsuccessful in these patients.

11. In ten of the patients, the successful surgical treatment of the pelvic lesion was followed by a disappearance of the gastro-intestinal complaint.

12. In two patients, surgical treatment of the pelvic lesion was refused, and these patients remained unimproved.

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SECTION II—*Experimental Physiology*

The Composition of Human Gastric Juice Secreted in Response to Histamine Administration*

By

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THE investigation of the gastric mucosa of mammalian animals presents great difficulties, owing partly to the very complex structure of the gastric mucous membrane—which includes several types of gland—and partly to the necessity of dealing with the secretions of all the gastric glands and epithelia, not separately, but as a mixture, which is referred to as "the gastric juice."

A great advance in the study of the secretory function of the gastric mucosa has been made in recent years. In this research histamine has proved a most useful agent. In the dog and cat, histamine presumably stimulates secretion in the parietal cells only. *The vagus nerve, on the other hand, influences the activity of the peptic as well as of the parietal cells.* Since no detailed study had ever been made of the two extremely different types of gastric juice obtained respectively by the administration of histamine and by sham-feeding, the writer has attempted an investigation of this problem. First of all, the effect of different types of stimuli on the composition of the gastric juice was studied in the dog, the results being reported elsewhere (Toby, 1936). In the present paper data obtained from a study of human gastric juice will be considered. Samples of gastric juice from normal human individuals and from several patients in the Royal Victoria Hospital, Montreal, were analysed. The same methods of analysis were used in these cases as in the animal experiments just referred to, so that a comparison could be made of the course and composition of the hydrolysed gastric secretion produced by histamine in such different species as man and the dog.

The literature concerning the study of gastric function presents a great mass of conflicting results. Some of the discrepancies would appear to be due to differences in experimental conditions or to faulty technique. Conclusions frequently have been based on clinical data alone, where the chances of error are greater than in the case of experimental animals. It is evident from experimental work on the dog that the general condition of the organism plays a great part in the response elicited by any given type of stimulus. Variations in the level of the blood chlorides, vitamin deficiencies, or changes in the proportion of the main constituents of the diet all influence the secretory activity of the stomach. Although the responses in the dog and the human respectively may not be identical even under approximately the same conditions, it *seemed desirable to compare data obtained on man with those already obtained on the dog, where a* greater number of factors could be standardized and where there was less likelihood of error or contamination in the collection of samples of gastric juice.

In brief, the results obtained by the writer (*l.c.*), using dogs with oesophagotomy and a gastric fistula, and a dog with a Heidenhain pouch, are as follows. The composition of the gastric juice varies according to the stimulus employed, which may act selectively on different groups of cells in the gastric mucosa. Two extremely different types of gastric juice are obtained after subcutaneous injection of histamine and after sham-feeding or pilocarpine injection. In the former case the juice is poor in organic material and enzymes, in the latter very rich in these constituents. There is, however, little difference in the total chloride concentration and total acidity of the gastric secretions produced by sham-feeding and histamine respectively. When pilocarpine is used as a stimulus, the total acidity of the secretion is markedly lower and the concentration of total chloride a little lower than when sham-feeding or histamine is employed. At times practically all the chloride present is in the form

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TABLE I

Total volume and average concentration of various constituents of the gastric juice for the whole secretory period after repeated subcutaneous injection of histamine or repeated 5-minute sham-feeding with meat in two dogs ("S" and "B") with œsophagotomy and gastric fistula.

Animal and Stimulus	Duration of secretion min.	Vol. c.c.	Mucus c.c.	Free HCl mg. %	Total acid (as HCl) mg. %	Total Cl mg. %	Neutral Cl (determined) mg. %	Neutral Cl (calculated) mg. %	Mucin (as glucose) mg. %	Total N mg. %	Pepsin Mett's units
Dog "S": Histamine	97	237	0.9	487	553	570	32	32	1.6	14.5	6
Dog "S": Sham-feeding	110	166	7.6	408	536	571	52	48	20.7	44.8	180
Dog "B": Histamine	125	132	0.2	361	510	567	—	41	—	19.0	16
Dog "B": Sham-feeding	111	143	3.5	418	555	570	—	35	—	47.0	219

of HCl. These slight variations in the total chloride are probably due either to contamination of the secretion *from the parietal cells with varying amounts of* fluid less rich in chlorides, secreted by other groups of cells, or, to a less extent, to changes in the concentration of chlorides in the blood plasma. Under the influence of any one stimulus, the gastric glands produce a secretion in which the acidity runs more or less closely parallel to the total chloride concentration; but as soon as a new stimulus is superimposed on the first, or towards the end of the secretory period, there is an alteration in the activity of different cellular groups and the acid and chloride are no longer secreted in parallel concentration. Since the volume and the total chloride content of the secretion vary little under different stimuli, whereas the organic content may be ten to twenty times greater than the minimum, it was concluded that the major part of the chlorides and the fluid of the gastric juice is produced by the parietal cells.

In order to facilitate the comparison of the data obtained on the dog with those relating to the composition of human gastric juice, an abbreviated table is given here of average results reported in the above-mentioned work (Table I).

METHODS

The persons to whom histamine injections were given, for the purpose of obtaining samples of gastric juice, were grouped as follows:

(1) Subjects with normal gastric function:
  (a) young men (students),
  (b) selected from among hospital patients;
(2) Patients with the under-noted gastro-intestinal diseases:
  (a) gastritis, functional diseases of the stomach, etc.,
  (b) gastric ulcer,
  (c) duodenal ulcer.

The last meal before the test was always taken on the previous evening. In the morning, the fasting juice was removed from the stomach. 0.5 to 1.0 mg. of histamine (ergamine acid phosphate) was then injected subcutaneously and gastric juice aspirated at 10- or in some cases 15-minute intervals, over a period of 60 to 80 minutes. Contamination with saliva was avoided as far as possible. Samples which, owing to duodenal regurgitation, were either dircolored with bile or abnormally large in volume, were discarded. As gastric juice may have passed into the duodenum between aspirations, the figures for the total amounts secreted must be considered as approximate. The volumes for the ten-minute intervals may also be somewhat inaccurate, as in some instances the aspiration was not complete. Smoothness and regularity of the volume curves would tend to make the aspirations appear complete.

The analytical methods employed were the same as those which served in the investigation of canine gastric juice (Toby, *l.c.*), this providing a good opportunity for comparing the composition of the gastric secretion in man and in the dog.

The total and free acidities of the juice were determined by titration with 0.01 N NaOH, phenolphthalein and Töpfer's reagent being employed as indicators. The salmon pink end-point for free HCl, suggested by Michaelis, was used. The total chloride was determined by Wilson and Ball's (1928) modification of Van Slyke's method and expressed as Cl, and the neutral chloride was estimated by ashing the juice and then determining the chlorides by the same method. The neutral chloride values were checked by calculating the difference between the total chloride and the Cl of the HCl. The variations were within the limits of experimental error.

The mucin was estimated by determining the reducing power of the juice by the Hagedorn and Jensen method (Peters and Van Slyke, 1932) after acid hydrolysis, the result being expressed as glucose. Reducing substances were also determined in the unhydrolysed juice, and this value was subtracted from that obtained after hydrolysis, so that the final figure represented glucose split from the mucoprotein.

The pepsin was determined by Nirenstein and Schiff's modification of Mett's method (Hawk and Bergeim, 1927).

The total nitrogen was estimated by digesting the juice by Kjeldahl's method, distilling the NH_3 in a modified Parnas-Wagner micro-Kjeldahl apparatus, and titrating with 0.01 N NaOH (Hawk and Bergeim, 1927).

RESULTS

Normal subjects. The composition of the gastric juice obtained after histamine injection was investigated in three young, normal subjects (Cases 1, 2 and 3). Of these control cases, No. 3 was rejected, since the samples showed a definite anacidity. In this apparently healthy young man the average total acidity of the gastric juice was rather low (125 mg. per cent), the total chloride content amounted to only 372 mg. per cent, and the neutral chloride to 243 mg. per cent (thus forming 64 per cent of the total chloride). The peptic power, however, was high, averaging 1115 Mett's units.

A complete analysis of the gastric juice in Case 1 is given in Table II by way of example. The average

TABLE II

Volume and concentration of various constituents of gastric juice in Case 1 (normal human subject). Histamine (0.5 mg.) injected subcutaneously. Samples collected at 10-minute intervals.

Sample No.	Vol. c.c.	Mucus c.c.	Free acid (as HCl) mg. %	Total acid (as HCl) mg. %	Total Cl mg. %	Neutral Cl mg. %	Total solids gm. %	Organic material gm. %	Ash gm. %	Total N mg. %	Mucin (as glucose) mg. %	Pepsin Mett's units	Remarks
0	27.5	2.1	18	117	337	223	1.12	0.64	0.48	96.3	64.6	1936	Fasting secretion. This and all the other specimens were clear.
1	16.5	2.0	37	139	357	222	1.10	0.62	0.48	92.4	66.8	2304	Histamine injected.
2	23.0	3.8	219	317	479	171	0.94	0.56	0.38	73.9	57.4	1600	
3	27.0	3.0	372	460	556	109	0.62	0.34	0.28	52.1	32.8	1600	
4	21 0	1.5	387	459	545	99	0.54	0.28	0.26	44.2	44 0	2025	
5	19.0	1.4	387	475	542	80	0.56	0.34	0.22	51.5	33.6	1024	
6	10 5	1.9	321	406	509	114	0.80	0.50	0.30	67.8	50.2	784	
7	8.0	1.5	241	340	471	140	0.96	0.62	0.34	89.0	53.4	1764	
8	2 0	0.4	226	329	—	—	——	——	——	——	——	——	
Average concentration, estimated on total secretion (130 c.c.)		1.9	273	377	510	132	0.77	0.46	0.31	67.3	48.3	1603	

figures for the whole secretory period in Cases 1 and 2 are shown in Table III. The gastric juice of four hospital patients, who were considered to have normally functioning stomachs, was also investigated. The latter have been included in the normal group, but with certain reservations on account of the unnaturally wide variations in volume, the low level of total chloride and total acid, and the abnormally high neutral chloride content of the juice.

The following conclusions may be drawn from a comparison of Cases 1 and 2 with the data obtained from the experiments on dogs (see Table I). The total acidity of the "histamine" gastric juice in humans (377 and 447 mg. per cent) is somewhat lower than in dogs with oesophagotomy and gastric fistula (553 and 510 mg. per cent) but somewhat higher than the "histamine" juice obtained from a dog with a Heidenhain pouch (436 mg. per cent). In two of the samples of juice from Case 2, the free acidity amounted to 424 and 438 mg. per cent respectively, thus approaching or equalling the values obtained in dogs. The average total chloride values (510 and 553 mg. per cent) approximated to those found in the "histamine" juice of two dogs (570 and 567 mg. per cent). Since in humans it is difficult to prevent entirely the contamination of the gastric juice with saliva, although this can be done in dogs with oesophagotomy, the small divergences in the acid concentration of human and canine gastric juice are to be ascribed to this rather than to differences in the secretory properties of the gastric mucous membrane in the two species. That it is highly important to exclude the possibility of contamination of the gastric juice by mouth secretions has been shown by Carlson (1919) in experiments on human subjects. Carlson found that the gastric juice obtained through a fistula had higher free and total acidity in cases of oesophageal obstruction (0.40 and 0.48 per cent) than in cases where the oesophagus was patent (0.34 and 0.44 per cent). It would seem safe to conclude therefore that there is little difference in the acid-producing properties of the gastric mucosa in dog and man.

Further observation, however, shows that normal human gastric juice and canine gastric juice are not alike in all respects. In the first place, we saw that the values for neutral chloride are much higher in normal human "histamine" juice (132 and 103 mg. per cent) than in the juice of dogs with oesophagotomy and a gastric fistula (32 and 41 mg. per cent). Only in the dog with a Heidenhain pouch was the concentration of neutral chloride (137 mg. per cent) observed to approach that of human gastric juice. It is possible that continuous irritation of the mucosa of the pouch by the drainage tube may have been partly responsible for this augmentation of the neutral chloride.

The difference in the concentration of neutral chloride in the normal human and in canine gastric juice may perhaps be explained by the fact that in the fundic part of the stomach the proportion of mucoid cells ("chief cells of the neck") to peptic cells is much greater in the human than in the dog (cf. description, drawings and photomicrographs in Zimmermann, 1925; Plenk, 1932; Bowie and Vineberg, 1935).

Next, the organic constituents must be compared. The values for total nitrogen, dissolved mucin and pepsin are undoubtedly much higher in human gastric juice elicited by histamine than in canine gastric juice produced by the same stimulus. In the dog, the amounts of mucin and pepsin secreted are practically negligible, and the nitrogen concentration is only about one-fourth that of the gastric secretion in the human. Again, samples of secretion from a Heidenhain-pouch dog had a much higher nitrogen content, although still only about half that of human gastric juice.

Especially striking is the extremely high concentration of pepsin in samples from some of the human

TABLE III

Average concentration of various constituents of the gastric juice estimated on the total secretion elicited by subcutaneous injection of histamine in normal and pathological individuals.

Case No.	Histamine injected mg.	Vol. c.c.	Mucus c.c.	Free acid (as HCl) mg. %	Total acid (as HCl) mg. %	Total Cl mg. %	Neutral Cl mg. %	% of total Cl present as neutral Cl	Total solids gm. %	Organic material gm. %	Ash gm. %	Total N mg. %	Mucin (as glucose) mg. %	Pepsin Mett's units	Remarks
1	0.5	130	1.90	273	377	516	132	26	0.77	0.46	0.31	67.3	48.3	1603	Normal
2	0.5	155	1.40	367	447	553	103	19	—	—	—	—	39.8	—	
7	0.5	98	0.80	0	71	151	101	67	0.53	0.24	0.29	37.3	25.9	307	Pathological (see footnote)
8	0.5	120	5.10	0	63	302	250	83	0.90	0.47	0.46	60.6	29.2	526	
10c	0.6	59	0.80	116	219	492	270	54	1.13	0.64	0.47	91.3	—	479	
10d	0.5	57	0.45	136	257	491	233	48	1.01	0.57	0.43	86.4	45.9	370	
12	0.7	54	0.17	68	172	370	203	54	1.07	0.72	0.35	85.3	36.3	1045	
13	0.8	62	2.58	58	148	324	192	59	0.82	0.46	0.36	67.3	33.6	256	
14	0.5	83	3.20	50	180	355	196	55	0.68	0.32	0.35	63.2	24.5	585	
15	0.5	108	2.70	0	83	291	209	72	0.97	0.55	0.42	77.5	28.2	690	
16	0.5	125	2.80	42	141	320	183	57	0.89	0.50	0.38	72.3	25.1	937	
17	1.0	162	2.50	290	416	484	80	17	0.58	0.39	0.19	57.7	29.8	178	
18	1.0	258	0.20	205	365	516	160	31	0.63	0.36	0.28	54.3	37.8	788	
19	0.5	317	0.30	268	394	530	147	28	0.54	0.28	0.26	63.2	23.1	624	

Note.
Case 7: diverticulum of greater curvature; neurasthenia.
Case 8: chronic gastritis; peritoneal adhesions (?); suspected gastric ulcer.
Case 10: gastric ulcer on lesser curvature.
Case 12: gastric ulcer.
Case 13: gastric ulcer (?).
Case 14: pyloric ulcer with obstruction.
Case 15: ulcer on lesser curvature.
Case 16: gastric ulcer (?); hematemesis; flattened duodenal cap.
Case 17: duodenal ulcer, penetrating and walled off
Case 18: duodenal ulcer polycythemia.
Case 19: duodenal ulcer.

subjects. Pepsin sometimes reached single values as high as 2304 and 2025 Mett's units, while averages might be as high as 1603 and 1115. Such values cannot always be obtained even by electrical stimulation of the vagus in acute experiments on dogs.

Several tentative explanations of this fact are here advanced. It might be suggested that: (1) In man histamine acts upon the peptic as well as upon the parietal cells, although in the dog and cat it only affects the latter. In that case histamine would be one of the strongest stimulants of the peptic cells in man. That this explanation is untenable, however, will be shown in the paper immediately following (Toby (2)). Human peptic cells produce a stronger protease than do the peptic cells of the dog and cat. (3) There is perhaps in the gastric mucosa of man a relatively greater number of peptic cells than in the gastric mucosa of the dog and cat. It has been shown by Aschoff (1923) and by Dr. D. J. Bowie (in a paper presented to the American Anatomical Society in April, 1936—personal communication) that in the dog and cat the peptic cells occupy the basal part of the gastric tubules. The rest of the tubule is lined with mucoid cells ("chief cells of the neck") and parietal cells. The peptic cells are most numerous in the glands of the fundic part of the stomach and less abundant in those nearer to the pyloric part. In the "intermediary zone" *("Zwischenzone")* of Aschoff the tubules contain only mucoid and parietal cells. In man the arrangement of the cells may be different; it is possible that there may be a larger proportion of peptic cells in some regions of the human gastric mucosa than in the corresponding regions of the canine gastric mucosa, or that the cells may be distributed more evenly throughout the entire fundic portion of the stomach in the human.

The relative difference in the amount of histamine administered to dogs and to human subjects must also be taken into consideration. The dogs received far larger doses in proportion to their body weight. Dogs of about 15 kg. received 0.75 to 1.0 mg. of histamine. Human subjects weighing 60 to 70 kg. received only 0.5 to 1.0 mg., or proportionately about one-fifth the amount administered to dogs. Since in the dog histamine acts almost exclusively on the parietal cells, the concentration of pepsin in the gastric juice secreted in response to applications of this substance will diminish as the volume of fluid increases. This is the so-called "washing-out" effect described by Babkin (1930).

In Cases 1 and 2, the free acidity of the juice remained high almost to the end of the secretory period. The total chloride content and total acidity were somewhat lower in the last samples, when the flow of gastric juice had greatly diminished. This is not in agreement with the finding of MacLean *et al* (1928a, b, c) that towards the end of the secretory period a neutral fluid is produced which replaces the acid secretion of the gastric glands. On the contrary, it would appear more likely from the results obtained by the writer (Toby, *l.c.*) and from the work of others (Webster, 1929; Bolton and Goodhart, 1931, 1933, and Hollander, 1934) that the neutralization of small amounts of acid juice present in the stomach is effected by the alkaline mucus secretion.

Thus, the gastric juice secreted by the normal human stomach, in response to a comparatively small dose of histamine, differs little in its acid properties from canine gastric juice, although it is richer than the latter in all the organic constituents and in neutral chloride.

Pathological Cases. Table III shows the volume of gastric secretion and the average concentration, for the whole secretory period, of its various components, determined in a representative number of patients suffering from various forms of gastro-intestinal disease, as well as in two normal cases (Nos. 1 and 2). In all the cases of gastric dysfunction without exception the total acidity was lower than in the normal cases, and only on a few occasions did it even reach half the concentration noted in the latter. In several cases the free acidity was zero, or very low. The total chloride concentration in a few of the cases studied was close to normal (*e.g.*, 492 and 481 mg. per cent), while in most of the others it was decidedly below normal. The neutral chloride concentration in all the cases of gastric dysfunction was above normal, with one exception (Case 7). In addition, the proportion of neutral chloride to total chloride was in all cases much higher than usual.

In Case 7 (diverticulum and functional disorder of the stomach) the neutral chloride content was low (101 mg. per cent), as was also the total chloride content, so that the proportion of chloride as neutral chloride was relatively very high (67 per cent). The peptic power of the juice was low. Undoubtedly in this case the activity of both the parietal and the peptic cells was depressed. It seems probable that the mucosa secreted a small amount of acid fluid which was partly neutralized and partly diluted by another secretion having a lower concentration of neutral chloride. The juice contained a fairly large amount of dissolved mucin (26.9 mg. per cent), which might have come from either the peptic or the mucoid cells. Again, there is the possibility that the parietal cells might have lost their ability to concentrate chloride, so that, although the volume of fluid passing through them might be as great as ever, the chloride concentration of the juice would be below normal.

The three cases of duodenal ulcer (Nos. 17, 18 and 19) gave results somewhat different from those of the cases in which the stomach was affected. In response to 1.0 mg. or even 0.5 mg. of histamine the gastric glands produced a juice in which the free and total acidities and the total chloride content were very high. The proportion of neutral chloride to total chloride approximated to that observed in the normal cases (Nos. 1 and 2).

DISCUSSION

From experimental data obtained on canine gastric mucosa it appears evident that the main functions of the parietal cells are to concentrate chloride to a level above that of the chloride in the blood and to convert it into hydrochloric acid. This is borne out by the analyses of the gastric juice of normal human subjects described in the present paper. The only difference between the composition of human gastric juice and that of canine gastric juice in respect to chloride content is that the former is somewhat richer in neutral chloride than the latter. All the gastric pathological cases examined by the writer showed impairment of one or both of these functions. This is well illustrated (see Table III) in one case of chronic gastritis (No. 8) and six cases of gastric ulcer (Nos. 10, 12, 13, 14, 15 and 16). In all these cases the total acidity is very much below normal, and in all but one (No. 10) the total chloride content is well below normal, while the neutral chloride in all cases is above normal. The volume of secretion is in several cases (Nos. 8, 15 and 16) approximately as great as in normal subjects. In the other cases it is markedly reduced (Cases 10, 12, 13 and 14).

If it be admitted that in the human gastric mucosa the greater part of the chloride and the fluid of the secretion are produced by the parietal cells, as is the case in the canine gastric mucosa, then it is conceivable that in the above instances the parietal cells lost first, their ability to convert neutral chloride into hydrochloric acid, and later, their ability to concentrate chloride. This explanation would be in agreement with Rosemann's theory, recently upheld by Katsch, Baltzer and Brink (1934), that the variations in the acidity of the gastric juice are due to the varying concentration of the HCl secreted by the parietal cells. Although the levels of total acid, total chloride and neutral chloride vary widely from case to case, the percentage of the total chloride present as neutral chloride is more or less constant and well above normal (see Table III). Two normal cases show respectively 19 and 26 per cent of neutral chloride; five gastric ulcer cases, 48 to 59 per cent; and one gastric ulcer case as much as 72 per cent. One case of diverticulum of the greater curvature, with functional disease of the stomach, and one of chronic gastritis show 67 and 83 per cent respectively. In contrast to these, and falling more or less within the normal range, are three duodenal ulcer cases in which the concentrations of neutral chloride are respectively 17, 28 and 31 per cent of the total chloride concentration.

Another tentative explanation of the deviations from normal observed in the composition of the gastric juice in pathological cases might be put forward, namely, that under the influence of a pathological process the secretory activity of different cellular groups included in the gastric glands only changes quantitatively as a rule. This explanation would accord with the theory, originating from this laboratory, concerning the regulation of the secretory activity of compound glands, such as the gastric glands (Babkin, 1931, 1934). Thus it might be that the amount of normal acid secretion produced by the parietal cells was greatly diminished in the cases in question, whereas the activity of those cells—mucous cells, "chief cells of the neck," peptic cells—which discharge a slightly alkaline secretion, containing a comparatively low concentration of neutral chloride, was markedly increased. Since the visible mucus in the gastric juice varied greatly from patient to patient, and the concentration of pepsin in the gastric secretion of the various cases could not be related to the concentration of neutral chloride, it is reasonable to assume that the chief source of the fluid containing the neutral chloride was neither the surface epithelium cells nor the peptic cells. Thus the mucoid cells ("chief cells of the neck") seem to be the most probable source of the neutral chlorides and base. Unfortunately we have no direct proof of this assumption, although it seems to be a reasonable one. There is as yet no proper method for ascertaining the degree of activity of the mucoid cells. The mucin which is dissolved

in the gastric juice probably arises both from the mucoid and the peptic cells. Therefore in pathological cases the concentration of mucin in the juice cannot be used as an indication of the functioning of the mucoid cells. In normal animals the values for pepsin, mucin and organic material practically parallel each other throughout the duration of the secretion. In the human cases of gastric dysfunction here studied the parallelism between these constituents occurred irregularly or was absent altogether, according no doubt to the extent to which the functions of different groups of cells were impaired.

Teorell's (1933, 1935) "diffusion theory" does not satisfactorily explain the altered properties of the gastric juice in cases of gastric dysfunction (see Table III). According to this theory the neutralization of HCl in the stomach is effected not by an alkaline secretion but by means of an interchange between the H ions of the juice and the Na ions of the tissue fluid. In the majority of our cases, not only was the total acidity of the juice diminished, but also the total chloride concentration. In terms of Teorell's theory, this phenomenon would be due to the fact that not only the H ions but Cl ions likewise are diffused back extremely rapidly into the tissue. It is very doubtful that this could occur in the freshly secreted gastric juice during the short interval of 10 to 15 minutes between two aspirations.

There is no evidence that in any of the pathological cases studied the acid gastric juice was neutralized at the height of its secretion by the alkaline pyloric juice. If this were so, an exceedingly great hypersecretion of pyloric juice would have to occur.

The limited number of pathological cases examined during this investigation does not justify the adoption of either of the explanations suggested above. However, the detailed study of the gastric secretion in these cases has yielded important information concerning the abnormal functioning of different groups of secretory cells which participate in the formation of the gastric juice. By following up this line of investigation it may be possible in the future to localize the exact seat of the pathological process in the gastric mucosa.

SUMMARY

1. Normal human gastric juice secreted in response to histamine administration is in many respects similar both qualitatively and quantitatively to canine gastric juice obtained by means of the same stimulus.

2. The concentrations of acid and total chloride in human gastric juice approximate very closely to those found in canine gastric juice. They remain more or less constant during the greater part of the secretory period but diminish as the secretion becomes less.

3. There is a higher concentration of neutral chloride in normal human gastric juice than in canine gastric juice. A considerable amount of organic material (*e.g.*, mucin, pepsin) as well as of nitrogen is always present in the former.

4. In all the pathological cases studied, in which an impairment of the gastric secretory function might be presumed, the gastric juice showed a smaller concentration of total chloride, and a greater concentration of neutral chloride, than under normal conditions. In most cases the volume of the secretion was reduced, and also the concentrations of free and total acid.

5. In the cases of duodenal ulcer investigated there was a tendency to hypersecretion of the gastric juice; the total chloride content of the juice was high; the percentage of total chloride present in the juice as neutral chloride was approximately normal, and the acidity was fairly high.

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Does Histamine Stimulate the Secretory Activity of the Peptic Cells in Man?*

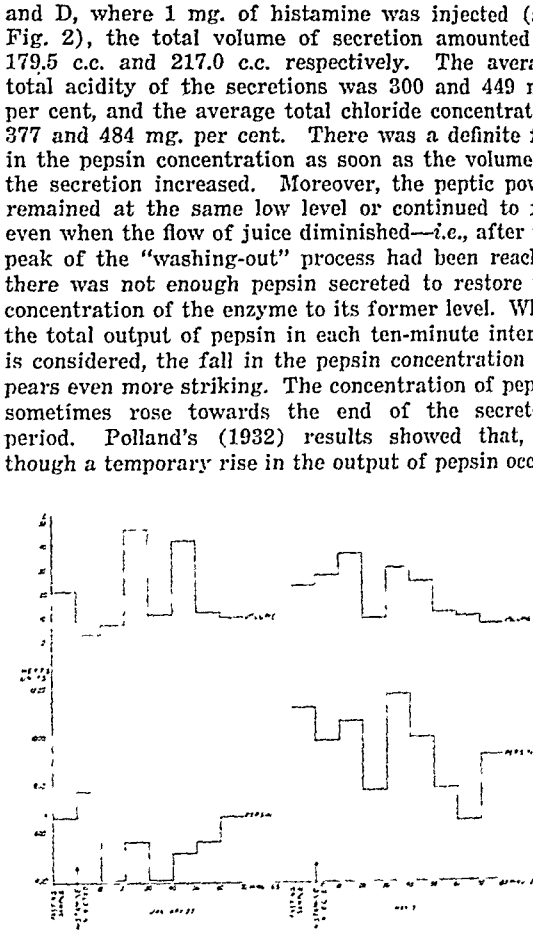
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IT has been shown by previous investigators who have studied the effect of histamine on the gastric glands in the dog and cat (Babkin, 1930; Vineberg and Babkin, 1931; Gilman and Cowgill, 1931; Baxter, 1934; Bowie and Vineberg, 1935) that this substance stimulates secretory activity in the parietal cells exclusively. Moreover, it seems probable that under certain circumstances histamine inhibits the secretory activity of the peptic cells (Alley, 1935).

During an investigation recently carried out by the writer (Toby, 1936) numerous examples of the selective action of histamine on the parietal cells of the canine gastric glands were obtained. It was found that in the dog histamine in the doses employed did not stimulate the discharge of pepsin. However, a great many clinicians hold that the administration of histamine in man results in an increased output of pepsin (Polland, 1932; Bloomfield and Polland, 1933; Blakely and Wilkinson, 1933; Rivers, *et al*, 1936; Osterberg, *et al*, 1936). They disagree with the view, held by many of the experimental physiologists working on animals, that only the parietal cells are actively engaged in secretion after histamine administration and that pepsin is merely "washed out" from the glandular tubules into which it is slowly and continuously discharged from the peptic cells.

This apparent difference in the effect of histamine stimulation of the gastric glands in the dog or cat as compared with man might be attributable to one of the following causes: (1) the mechanism regulating the secretory activity of the gastric glands in man may be fundamentally different from that in carnivorous animals, or (2) the experimental conditions and the methods of stimulation employed may have been such as to give different results. It was decided to test out the latter of these two assumptions as being the easier of attack. As has been mentioned in the preceding paper (Toby), the doses of histamine administered to animals were much larger than those usually administered to man (i.e., 0.50 to 0.66 mg. per 10 kg. body weight in the dog as compared with 0.10 mg. or less per 10 kg. body weight in man). Mrs. M. M., who was a patient in the Royal Victoria Hospital, Montreal, for several months, suffering from ulcer on the lesser curvature of the stomach near the esophagus, provided an opportunity for studying repeatedly the effect of both small (0.5 mg.) and large (1.0 mg.) doses of histamine on the gastric secretion.

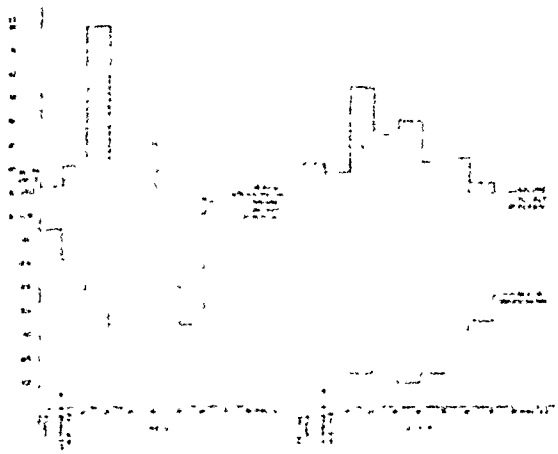
From a great number of analogous experiments carried out on this patient, four have been selected (A, B, C and D). In A and B the secretory effect of 0.5 mg. of histamine may be seen, and in C and D the effect of 1.0 mg. of histamine. The course of the gastric secretion and the concentration of pepsin in each case are represented graphically in Figs. 1 and 2. The usual small dose of histamine (0.5 mg.) was given in Tests A and B (see Fig. 1) and provoked the secretion of respectively 139 c.c. and 161 c.c. of gastric juice, in which the average total acidity (382 and 333 mg. per cent) and the average concentration of total chloride (505 and 457 mg. per cent) were moderately high. The peptic power of the juice was moderate in A, and rather higher in B. There was a tendency in both instances for the pepsin to diminish with the increase in the volume of the secretion. In Tests C and D, where 1 mg. of histamine was injected (see Fig. 2), the total volume of secretion amounted to 179.5 c.c. and 217.0 c.c. respectively. The average total acidity of the secretions was 300 and 449 mg. per cent, and the average total chloride concentration 377 and 484 mg. per cent. There was a definite fall in the pepsin concentration as soon as the volume of the secretion increased. Moreover, the peptic power remained at the same low level or continued to fall even when the flow of juice diminished—*i.e.*, after the peak of the "washing-out" process had been reached there was not enough pepsin secreted to restore the concentration of the enzyme to its former level. When the total output of pepsin in each ten-minute interval is considered, the fall in the pepsin concentration appears even more striking. The concentration of pepsin sometimes rose towards the end of the secretory period. Polland's (1932) results showed that, although a temporary rise in the output of pepsin occur-



A B

Fig. 1. Relation of concentration of pepsin to fluid volume in gastric secretion produced by 0.5 mg. histamine. (Case "M. M.": Tests A and B).

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Submitted October 16, 1936.



C D

Fig. 2. Relation of concentration and total output of pepsin to fluid volume in gastric secretion produced by 1 mg. histamine. (Case "M. M.": Tests C and D).

red after each injection of histamine, there was a definite fall in the pepsin concentration during the course of the experiment, as may be seen in all his four charts.

The only interpretation that might be put upon these data would seem to be that *histamine is a selective stimulus* which acts exclusively on the parietal cells, or at least much more strongly on them than on those concerned with the elaboration of pepsin. Further confirmation of this is afforded by the fact that the greater the volume of the secretion, the higher is the acidity and the lower the organic and enzymatic content of the juice.

It must be borne in mind that in all the cases investigated by the writer (see also preceding paper) there was a "spontaneous" secretion of gastric juice before the histamine was injected. The histamine secretion was superimposed on this spontaneous secretion, and was diluted by it. The peptic power of the spontaneous juice differed very much in the various cases and in some of the specimens it was fairly high. Hence in experiments on man the pepsin output cannot be taken as an indication of the effect of histamine on the peptic cells, although it has been considered as such by several clinical investigators (*e.g.*, Polland, 1932; Bloomfield and Polland, 1933). Experiments on man do not present so clear a picture in this respect as do animal experiments, since in the latter there may be no secretion for a very long time before histamine is administered and the true effect of histamine on the resting gastric glands may be observed.

The following figures show how important it is to determine the peptic power of the "fasting" juice in order to arrive at a proper evaluation of the histamine test in man. In the so-called "fasting" gastric juice of the subjects studied, all of whom were pathological cases except Case 1 (cf. Table III of the preceding paper), the peptic power was roughly of the same magnitude as the average peptic power of the "histamine" gastric juice of the same individual.

Peptic Power of Gastric Juice (in Mett's units)

Case No.	"Fasting" Juice	"Histamine" Juice
1	1936	1603
4	502	499
5	1024	1111
6	433	511
8	644	526
10c	256	479
12	1414	1045
15	400	690
16	1296	937
17	traces	178
18	701	788

If histamine stimulates the peptic cells, then in the gastric juice secreted after histamine administration, the values for pepsin should be more uniform, like those for the total chloride and hydrochloric acid, and the concentration of pepsin should always rise above the fasting level.

CONCLUSION

In the light of the data at our disposal, it seems reasonable to conclude that histamine does not augment the output of pepsin, and that "histamine" gastric secretion reflects the state of activity of the peptic cells before the injection of this substance. There seems to be no need therefore to suggest a new theory to explain the action of histamine on the human gastric glands. The conception formulated by previous investigators with respect to the gastric glands of carnivorous animals, namely, that histamine stimulates the parietal cells exclusively, may be safely applied to human gastric glands as well.

I have great pleasure in expressing my thanks to Dr. B. P. Babkin for his kind interest in this work and his most helpful criticisms and advice. I am indebted also to the Department of Experimental Surgery and Medicine of McGill University for facilities and assistance, and to Drs. John Armour and A. M. Vineberg of the Royal Victoria Hospital, Montreal, for making this investigation possible. I am obliged to Miss J. F. Oswald for assistance in the preparation of the manuscript.

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Gastro-Intestinal Studies

VI. The Volume of the Gastric Juice in Pernicious Anemia*

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IN a previous article (1) an attempt was made to correlate the findings in the gastric juice of 47 patients having pernicious anemia with the clinical condition of the patient, the degree of central nervous system involvement, and the maintenance dosage of liver extract. Little or no correlation could be found at that time. It was stated, however, that the patients who had lower red blood cell counts tended to have smaller volumes than those having higher counts. Also, the patients with early or no central nervous system involvement more often had greater volumes of gastric juice than did those with moderate to advanced central nervous system involvement.

Isaacs and Goldhamer (2) concluded that in pernicious anemia the deficiency in intrinsic factor is a quantitative rather than a qualitative deficiency. Goldhamer (3) stated that in patients with untreated pernicious anemia there is a direct relationship between the amount of gastric juice secreted per hour by the patient and the red blood cell level—that is, the greater the gastric secretion the higher the red blood cell level. He concluded that erythropoiesis depends in part at least upon the action of the intrinsic factor and that the rate of red blood cell formation is related to the amount of intrinsic factor produced.

METHOD OF STUDY

It is the purpose of this paper to present the findings in the gastric juice of 125 patients having pernicious anemia. A total of 160 examinations was made.

After removal of the fasting gastric contents each patient was given 0.5 mg. of histamine hydrochloride subcutaneously. The gastric secretions were then completely removed every 20 minutes for one hour. The patients were cautioned not to swallow any saliva during the time the tube was in place. The volume, pH, and rennet activity were determined on each specimen. The pH of the specimens varied between 7.2 and 8.6. There was practically no rennin in any of the samples.

The patients have been divided into three groups. Group I is made up of patients who were in relapse and had received no hematopoietic medication for at least 3 months. The patients in Group II had had some type of medication but the red blood cell counts were not normal; included in this group are 18 patients who were in blood relapse but who were excluded from the first group because they had recently received medication, such as iron or some oral liver preparation. All of the patients in Group III had been on medication and their red blood cell counts were normal.

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Table I shows the average findings of these three groups in addition to those of 18 normal individuals and of 38 patients having anacidity not associated with pernicious anemia. Before being grouped as easy or hard to maintain the patients were previously or have subsequently been followed for at least one year. Those patients able to maintain normal red blood cell counts while receiving daily 3 vials of powdered liver extract or 12 capsules of 'Extralin' (Liver-Stomach Concentrate, Lilly), or less, were classified as easy to maintain.

RESULTS

There were 58 untreated patients in Group I. Two of these patients were examined in two different relapses, making a total of 60 examinations. The volume of gastric juice per 60 minutes varied between 1 c.c. and 63 c.c., averaging 17.9 c.c. These values agree very closely with those of Goldhamer, as does the average secretion (136.4 c.c.) of the normal individuals. Examination of Chart I shows that while the patients having red blood cell counts below 1.50 million had the lowest average (13.8 c.c.) volume of gastric juice, there is no direct relationship between the volumes and the red blood cell counts. The average value for the 35 patients with red blood cell counts below 2.00 million was 17.3 c.c., while the average for the 25 patients with red blood cell counts above 2.00 million was 18.9 c.c. However, the patients with red blood cell counts below 2.00 million had a distinctly greater average age.

In this group the patients having only early cord changes had an average 60-minute volume of 18.4 c.c., while those with moderate to advanced cord symptoms had only 16.4 c.c. Twenty-four patients' red blood cell counts could be maintained at normal levels while taking medication by mouth. Their average 60-minute secretion was 22.7 c.c., as compared with 16.5 c.c. for the 14 patients who were hard to maintain. The most striking variation in the average volumes of gastric juice was, however, in the various age groups. Examination of Table II shows that in Group I there was a progressive decrease in average volumes with increase in age. There was a tendency for the older patients to have lower red blood cell counts, but when a total of 166 patients in relapse was studied, as to age and initial red blood cell count, this relationship was not evident.

Three patients in Group I are of especial interest. The first was seen in October, 1933, when the red blood cell count was 3.60 million and the hemoglobin 66 per cent. At that time the 60-minute volume of gastric juice was 11 c.c. The patient took 12 capsules of

TABLE I

The average volumes of gastric juice in Groups I, II, and III, miscellaneous anacidities, and normal individuals

Group	Ave. Age	No. Cases	Ave. c.c. G. J. in 60 min.	No. Cases	Ave. c.c. G. J. in 60 min. in patients with early or no C. N. S. involvement	No. Cases	Ave. c.c. G. J. in 60 min. in patients with moderate to advanced C. N. S. involvement	No. Cases	Ave. c.c. G. J. in 60 min. in patients easy to maintain	No. Cases	Ave. c.c. G. J. in 60 min. in patients hard to maintain
I	59	60	17.9	31	18.4	29	16.4	24	22.7	14	16.5
II	56	54	31.8	27	36.2	27	28.9	13	33.1	30	31.9
III	55	46	41.3	23	44.2	23	38.3	22	38.6	16	48.4
Miscellaneous anacidities	43	38	41.7								
Normals	30	18	136.4								

'Extralin' daily until December, 1933, and then discontinued the medication. By July 30, 1935, the red blood cell count was 1.72 million and the hemoglobin 46 per cent. The hourly gastric secretion was then 7 c.c. The second patient (age 76) on April 7, 1933, had a red blood cell count of 1.45 million, hemoglobin of 38 per cent, and gastric secretion of 7 c.c. per hour. She received medication by mouth and injection up until August, 1934, and then voluntarily discontinued it. By March 19, 1936, the red blood cell count was down to 1.21 million and the gastric secretion was 8 c.c. per hour. The third patient first entered the hospital on January 15, 1935, when the red blood cell

TABLE II

The average volumes of gastric juice in the various age classifications in Groups I, II, and III

Age	*Group I*		*Group II*		*Group III*	
	No. Cases	Ave. c.c. G. J. in 60 min.	No. Cases	Ave. c.c. G. J. in 60 min.	No. Cases	Ave. c.c. G. J. in 60 min.
30 to 50	12	23.3	13	35.5	14	50.5
51 to 60	16	18.9	23	30.0	18	40.7
61 to 80	32	13.8	18	30.3	12	29.6

count was 0.5 million and the hemoglobin 12.2 per cent. Marked generalized arteriosclerosis was present and the patient was in severe cardiac failure. Following transfusion and liver extract administered intravenously the patient showed a marked improvement. On February 2, 1935, the red blood cell count was 2.43 million, hemoglobin 50 per cent, and weight 129 pounds. The total secretion of gastric juice for one hour was only 1 c.c. on that day. On March 26, 1935, the patient was discharged from the hospital with a month's supply of liver extract. He did not return again until December 2, 1935, when the red blood cell count was 1.98 million and the hemoglobin 62 per cent. At that time his general condition was good, he weighed 165 pounds and the gastric secretion was 9 c.c. per hour.

In Group II the average volume of the 54 examinations was 31.8 c.c., which is distinctly greater than the average of the untreated patients. However, Tables I and II show that the averages of the various subgroups tend to have the same relationship as in the untreated group.

One patient in this group is particularly interesting. In 1932 the patient was receiving liver extract by mouth and injection, yet the red blood cell count remained in the neighborhood of 4.50 million. At that time the patient was complaining that she could not gain weight (weight was 128 pounds). A urea clearance was 72 per cent of normal and the gastric secretion was only 8 c.c. per hour. Just before re-examination of the gastric juice in 1935, the patient suddenly began to gain weight (up to 140 pounds) and to feel better. The red blood cell count, however, remained at the same level. A urea clearance was repeated at about the same time and it was 97 per cent of normal. The secretion of gastric juice was then 30 c.c. per hour.

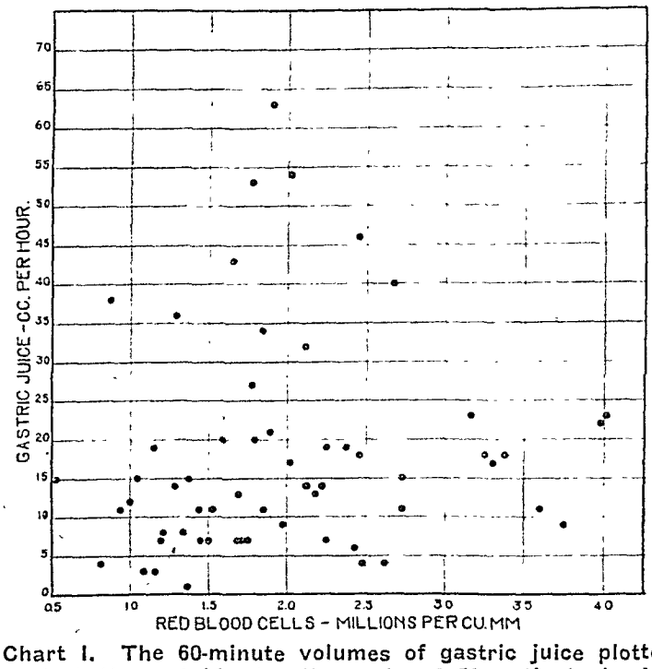


Chart I. The 60-minute volumes of gastric juice plotted against the red blood cell counts of 58 patients having pernicious anemia in relapse.

The *average values* of the 46 examinations in the 44 treated patients (Group III) are still higher, the average being 41.3 c.c., which is practically identical

with the average for the 38 examinations in patients with anacidity not associated with pernicious anemia. The findings as to central nervous system involvement and age in the two preceding groups are substantiated by this group. However, the 15 patients whose red blood cell counts were difficult to maintain at normal levels have a distinctly higher average than those whose blood could be maintained by oral therapy. This can be explained by the fact that the 28 patients with normal red blood cell counts who had received medication by injection averaged 47.8 c.c. of gastric juice per hour while the 16 patients who had received only oral therapy averaged 27.6 c.c. Only 5 of the patients in the easily maintained group had recently received intramuscular liver therapy, but all of the patients whose blood was difficult to maintain had received liver extract by injection.

The *effect of treatment on the volume of gastric juice* is brought out even more forsibly when the small group of patients is studied who were examined when the red blood cell count was below normal and reexamined after the blood improved. Twelve patients who were examined before and after oral therapy showed an average increase of 2.3 c.c., while the average increase in 17 patients after parenteral therapy was 15.7 c.c. The increase following parenteral therapy was more marked in the younger patients, but in all age groups there was a greater increase after parenteral therapy than after oral. The fact that 4 of the patients who showed definite increases in volume of gastric juice after parenteral therapy had relapses of the blood soon after returning to oral therapy, indicates that if this increase is associated with an increase in intrinsic factor it is not long sustained after discontinuing the parenteral therapy. Two patients whose volumes of gastric juice while receiving parenteral therapy were 88 c.c. and 67 c.c., respectively, have subsequently maintained normal red blood cell counts on oral therapy. Their volumes of gastric juice are now 64 c.c. and 44 c.c. per hour, respectively.

CONCLUSIONS

It would seem that the volume of gastric juice secreted after histamine stimulation by a patient having pernicious anemia is influenced by the general condition of the patient, the red blood cell level, the extent of central nervous system involvement, and the type of therapy the patient has received. Although there seemed to be no direct relationship between the volume of gastric juice and the red blood cell level at the time of relapse, the patients with lower red blood cell counts tended to have smaller volumes of gastric juice. The age of the patient appeared to have a more definite relationship to the volume of gastric juice, there being a progressive decrease in average secretion with increase in age. The patients having signs and symptoms of more advanced central nervous system involvement had a slightly lower average volume of gastric juice than did the patients having only minor involvement. The patients in relapse had distinctly lower 60-minute volumes than those patients under treatment. In addition, the type of therapy influenced the volume of gastric juice. In all the age groups the average secretions of the patients receiving liver extract by injection were higher than those of the patients receiving only oral therapy.

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Studies on the Chemical Nature of the Interaction Between the Intrinsic and Extrinsic Antianemic Factors Upon Incubation of Liver Extract and Normal Gastric Juice*

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EVIDENCE that liver substance is a potent source of the antianemic extrinsic factor of Castle has been brought out through the work of Reimann (1), Walden and Clowes (2), Helmer, Fouts and Zerfas (3), and others. Helmer, *et al* showed that daily subminimal doses of Liver Extract No. 343 (material derived from 100 grams of liver) after incubation at 40° C. with 100 c.c. of normal gastric juice produced maximum reticulocyte responses and marked clinical improvement in patients with pernicious anemia in relapse.

Therefore, since liver extract affords a readily available and fairly uniform source of extrinsic factor, we thought it would be of interest to determine whether a chemical change could be demonstrated when liver extract was incubated with normal gastric juice. Incubations were carried out under the same quantitative conditions used in successful clinical experiments; that is, one vial of Liver Extract No. 343 incubated with 100 c.c. of normal gastric juice. The components

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TABLE I

Titration of liver extract in formaldehyde after its incubation with gastric juice at pH 2.0, 5.6, and 8.0

Incubation pH	2.0		5.6		8.0	
Incubation time	0	3.5 hrs.	0	3.5 hrs.	0	3.5 hrs.
Titration (of 5 c.c. incubation mixture with 0.1 N NaOH)	7.89 7.88	8.00 7.91	4.50 4.52	4.52 4.53	2.89 2.90	2.90 2.90
Mean titration	7.89	7.96	4.51	4.53	2.90	2.90
Difference	0.07		0.02		0.00	
Difference per 100 c.c. gastric juice in m.-eq.	0.21 m.-eq.		0.06 m.-eq.		0	

TABLE III

Determination of the effect of incubation with gastric juice at pH 2.0 (Sample A), pH 5.6 (Sample B), and pH 8.0 (Sample C) on the soluble nitrogen content of liver extract

Sample	A		B		C	
Incubation pH	2.0		5.6		8.0	
Incubation time	0	3.5 hrs.	0	3.5 hrs.	0	3.5 hrs.
Soluble nitrogen per sample—mg.	1.081 ± .006	1.087 ± .009	1.403 ± .011	1.410 ± .001	1.386 ± .004	1.389 ± .004
Increase in soluble nitrogen per sample—mg.	0.006		0.007		0.003	

of liver extract that were studied were the amino nitrogen content, the acidity with the amino groups suppressed, and the soluble nitrogen content after precipitation with trichloracetic acid.

EXPERIMENTAL

The gastric juice used in these experiments was obtained from young, healthy adults after histamine stimulation. The aqueous solution of liver extract was prepared by shaking Liver Extract No. 343 in water, to which were added a few drops of toluene as a preservative, the proportions being adjusted so that 25 c.c. of the solution represented the soluble fraction of the amount of liver extract derived from 100 grams of whole liver (4.5 grams of powder).

The same incubation technique was employed for each experiment. The incubations were carried out in stoppered test tubes of appropriate size suspended in a water bath which was maintained at 40° C. The incubation mixtures consisted of one part of liver extract solution, four parts of gastric juice, and one part of HCl or NaOH solution, the proportions of the latter being calculated from a previously prepared titration curve of liver extract in such a manner as to fix the pH of one incubation mixture at 2.0, a second at 5.6, and a third at 8.0. The incubation time in each case was 3½ hours.

The study of the proteolytic action of normal gastric juice on liver at pH 2.0, 5.6 and 8.0 involved the following experiments:

1. Titration to a phenolphthalein end-point of 5 c.c. of each incubated mixture following the addition of 25 c.c. of 40 per cent formaldehyde, which was found experimentally to be sufficient to repress all amino groups. The control in this experiment was conducted by pipetting 5 c.c. portions into formaldehyde immediately after mixing the gastric juice and the liver extract solution. Any difference between the acidity of a sample and its control may be interpreted as measuring a liberation of carboxyl groups in incubation. Ten drops of 1 per cent phenolphthalein were used as an indicator and the titration performed in such a way that a direct color match was obtained between each incubated sample and its control. (Table I).

2. Determination by the manometric method of Van-Slyke (5) of the amino nitrogen content of the incubated mixtures and their controls, which consisted of mixtures containing HCl in place of gastric juice. An additional control consisting of pepsin (U. S. P. 1:3000) made up to contain 5 mg. of pepsin per c.c. of 0.1 N HCl was also utilized. These determinations were performed on 5 c.c. of a 4/25 dilution of the incubated mixtures. (Table II).

3. Determination of the nitrogen contained in the non-precipitated fraction of the incubated mixtures after treatment with an equal volume of 10 per cent trichloracetic acid, and, for controls, determination of the non-precipitated nitrogen of a portion of the same mixtures treated with trichloracetic acid immediately after mixing the gastric juice and the liver extract solution. The mixtures containing the trichloracetic acid were allowed to stand 12 hours in a refrigerator before they were filtered. The nitrogen determinations, performed by the manometic

TABLE II

The change of amino nitrogen on incubating liver extract with gastric juice at pH 2.0 (Sample A), pH 5.6 (Sample B), pH 8.0 (Sample C), and with pepsin-HCl solution at pH 2.0 (Sample D)

Sample (5 c.c. of 4/25 dilution)	A	A blank	B	B blank	C	C blank	D	D blank
Incubation pH	2.0	2.0	5.6	5.6	8.0	8.0	2.0	2.0
Amino nitrogen—mg.	0.626 ± .003	0.608 ± .000	0.596 ± .001	0.592 ± .001	0.593 ± .001	0.587 ± .001	0.594 ± .002	0.564 ± .001
Change in amino nitrogen—mg.	0.018		0.004		0.005		0.030	
Change in amino nitrogen per 100 c.c. of gastric juice—mg.-eq.	0.241		0.054		0.067		0.401	

method of VanSlyke (6), were made on 1 c.c. quantities of filtrate. (Table III).

RESULTS

As is evident from Table I, the only effect which may be interpreted as indicating a liberation of carboxyl groups occurred at pH 2, and, expressed quantitatively, it amounted to 0.24 milliequivalents. These figures were paralleled by the results of the amino nitrogen experiments (Table II), which indicated a liberation of 0.24 milliequivalents of amino nitrogen at pH 2 and only very small changes at pH 5.6 and 8.0. These phenomena occurring at pH 2 are felt to be explained adequately on the basis of the pepsin-HCl control experiment (Table II), the results of which indicated a change in amino nitrogen due to pepsin of 0.401 milliequivalents.

As shown in Table III, no change greater than the experimental error occurred in soluble nitrogen not precipitated by trichloracetic acid as a result of incubating liver extract and gastric juice at pH 2.0, 5.6 or 8.0 (Table III).

In addition to the above experiments, an experiment was performed with gastric juice from which all of the pepsin and rennin had been removed by treatment with Lloyd's reagent. Helmer and Fouts (7) have found that gastric juice so treated still contains the intrinsic factor of Castle. In the experiments using this pepsin-free intrinsic factor, no change in the amino nitrogen was obtained even when the incubation was carried out at pH 2.0.

DISCUSSION

Incubation together in vitro of the intrinsic and extrinsic anti-anemic factors, the result of which is presumably production of a material clinically active when fed to patients with pernicious anemia, effects no appreciable change that we have been able to measure in the content of carboxyl groups, amino nitrogen, or nitrogenous substances which are not precipitated by trichloracetic acid. Whether a change occurs which falls into the category of the chemical processes studied but smaller than our methods could elicit, or whether the nature of the phenomenon renders it not amenable to the chemical methods employed, is a matter for future study. There is the further possibility that some other biochemical factor, or factors, in addition to the one occurring in gastric juice, may be required for the formation of the final anti-anemic principle, particularly since the hemopoietic factor of the liver is heat-stable, whereas substances produced by the interaction of normal gastric juice and extrinsic factor are destroyed by boiling for five minutes. Furthermore, the antianemic principle of liver is effective when administered by mouth or parenterally, while, as yet, an effective parenteral preparation from the interaction of gastric juice with liver extract has not been made.

SUMMARY

Attempts have been made to determine the chemical change occurring as a result of incubation together of liver extract and normal gastric juice at pH 2.0, 5.6 and 8.0. The chemical constituents of liver extract which were studied were the carboxyl groups, amino nitrogen, and soluble nitrogen after precipitation with trichloracetic acid.

No significant chemical changes were noted in this series of experiments except for those associated with a slight proteolytic effect at pH 2.0, attributable to peptic activity.

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SECTION III—*Nutrition*

Protamine Insulin in the Treatment of Diabetes

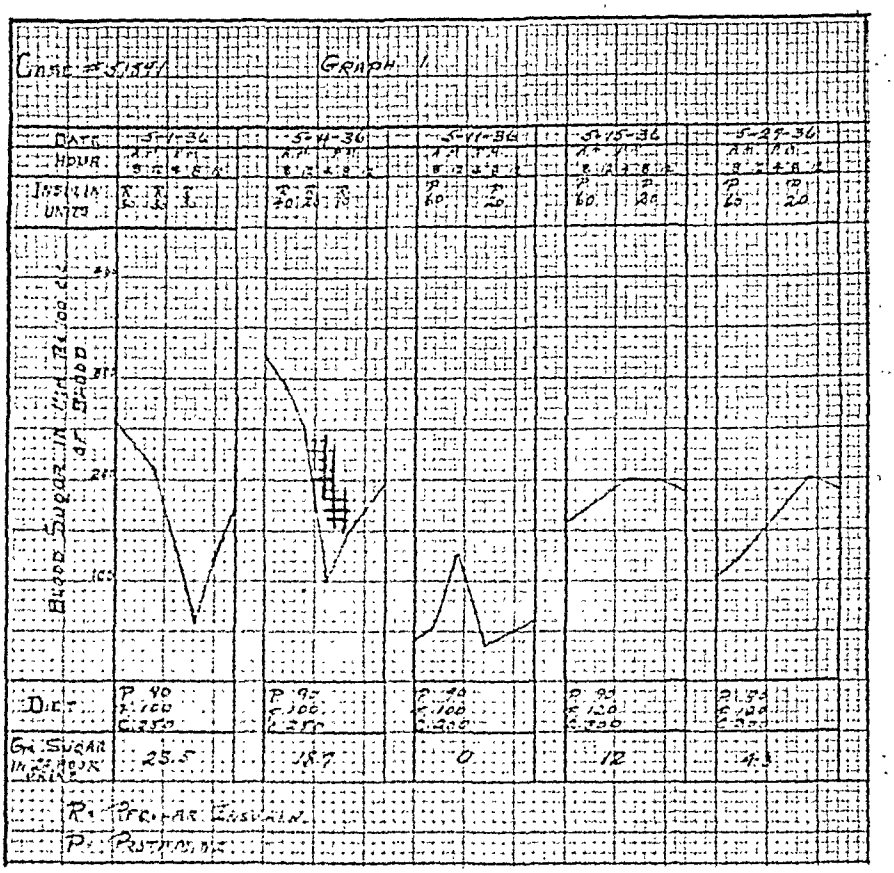
By

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PROTAMINE insulin is the precipitate formed by the action of insulin hydrochloride with monoprotamine compounds. It was first introduced by a group of Danish investigators (1), who were searching for a preparation which would give a more sustained lowering of the blood sugar than that obtained by the use of regular insulin. The protamine insulinate resulting from this precipitation, after being properly buffered, was found to be relatively insoluble in tissue fluids, causing the insulin to be liberated slowly and over a prolonged period of time. From our experience and from the reports (2) that have appeared in the short period of time, one gets the impression that this preparation if used wisely, may eventually prove to

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Case 1 (Graph 1) illustrates a moderately severe diabetic whose blood sugar showed marked fluctuations in spite of moderately large doses of regular insulin. The high calorie intake was necessary for the well being of the patient, who complained bitterly about the fact that he was constantly hungry. It will be noted that after a period of one week with the protamine insulin, these wide fluctuations in the blood sugar were considerably diminished and as time went on less protamine insulin became necessary for the control of these fluctuations. This is a representative example of the response of a diabetic patient where the protamine insulin is administered as two doses, one at 8 a.m. and the other at 8 p.m., allowing about two-thirds of the total insulin in the morning dose and one-third in the evening.

be a great advancement in the treatment of diabetes. On the other hand, its use without care or definite knowledge of its action, may produce harmful results and discredit the useful purpose for which it was intended.

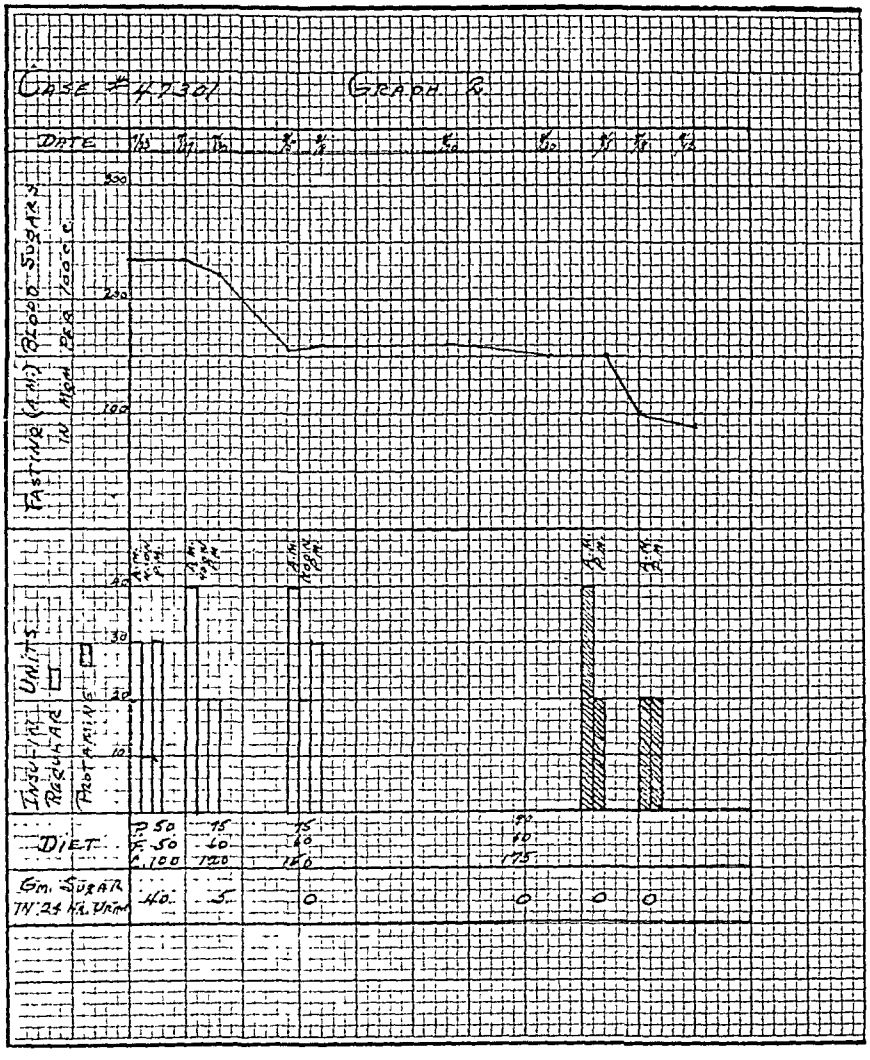
The new preparation as supplied for clinical trial, consists of a small vial containing the protamine to be added to 5 c.c. of U-50 insulin, thus resulting in a U-40 mixture. The solution is shaken thoroughly before each injection and administered subcutaneously. It is not to be used intravenously. When first introduced it was believed that this preparation remained stable for only three or four days and then had to be discarded if not completely utilized at the end of this period. Since then, further investigation has shown that the protamine insulin can remain effective for a period of four weeks.

Action of Protamine Insulin. When a dose of the protamine insulin, equivalent to a diabetic's usual insulin requirement, is injected into such a patient no effect is noted until four to six hours have elapsed. If food is withheld, hypoglycemia will set in at about the ninth hour and this state will continue up to about the thirty-ninth hour, producing usually the train of symptoms either of those associated with hypoglycemia or those associated with acidosis and impending coma.

Indications and Contra-Indications for Its Use. It stands to reason that any preparation having such a marked and prolonged effect, can produce a great deal of trouble if not properly administered. Likewise its use can be greatly discredited by its injudicious employment.

What the medical practitioner is anxious to learn is the exact type of case where this preparation may be of greater benefit than the regular insulin. As far as our experience permits us to judge at the present time, any case of diabetes which in spite of proper diet and adequate doses of regular insulin, shows marked fluctuations in the blood sugar with or without episodes of hypoglycemic reactions, constitutes the ideal indication for the use of the protamine insulin.

After considerable skill is obtained in the use of this preparation, the group of selective cases may be



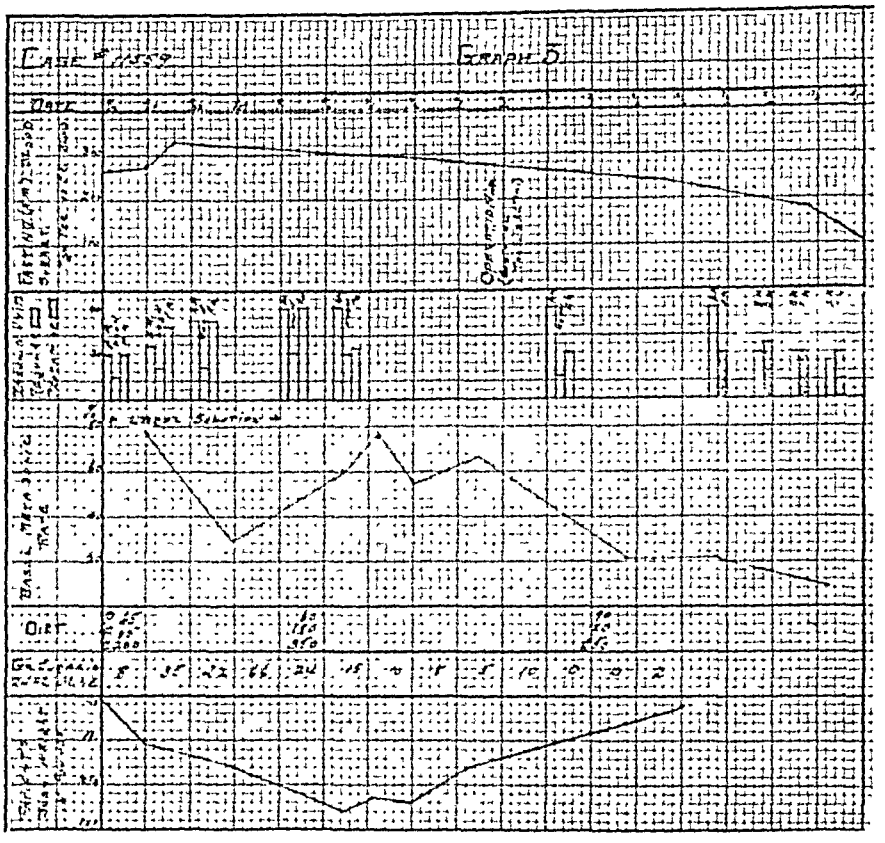
Case 2 (Graph 2) illustrates the case of a mild diabetic whose fasting blood sugar continued to remain elevated although he was sugar free. This condition was very easily corrected by changing to the protamine insulin, using a much smaller dose than that of the regular insulin. On a diet of P. 75 F. 60 C. 120 and regular insulin of 90 units he still persisted in showing a considerable hyperglycemia. Compare this with the increased diet of P. 90 F. 60 C. 175 and an intake of only 40 units of protamine insulin with the resultant disappearance of the persistent hyperglycemia. This shows an example of the procedure similar to that used in Case 1, but where the indication is not as urgent.

enlarged to include the average case of diabetes requiring insulin, where it is desired to obtain a more even blood sugar level during the twenty-four period, or where it is desired to diminish the amount of insulin, the frequency of injections, or both.

It must always be remembered that the protamine insulin has a delayed reaction-time and also that its action when once initiated in reducing the blood sugar continues to do so, over a much longer period than the regular insulin. This action immediately excludes cases of acidosis and impending coma, where quick action is demanded. Likewise new diabetic patients, about whom no observations are obtainable with the regular insulin, should not receive the protamine insulin as an initial method of treatment.

Calculation of Diet and Protamine Insulin Requirement. A practical way of calculating the diet for a patient who is to receive the protamine insulin may be briefly stated as follows: Allow one gram of protein and two and a half grams carbohydrate per kilo of body weight. Enough fat is then added to bring the caloric intake to the required amount. The carbohydrate is so distributed that one-fifth is received for breakfast, and two-fifths each for lunch and dinner. The diet used in Hagedorn's original cases, however, averaged only about 100 Gm. of carbohydrates which were divided into 40% each for breakfast and lunch, and 20% for dinner.

Regarding the actual calculation of the amount of protamine insulin necessary in a given case, one must

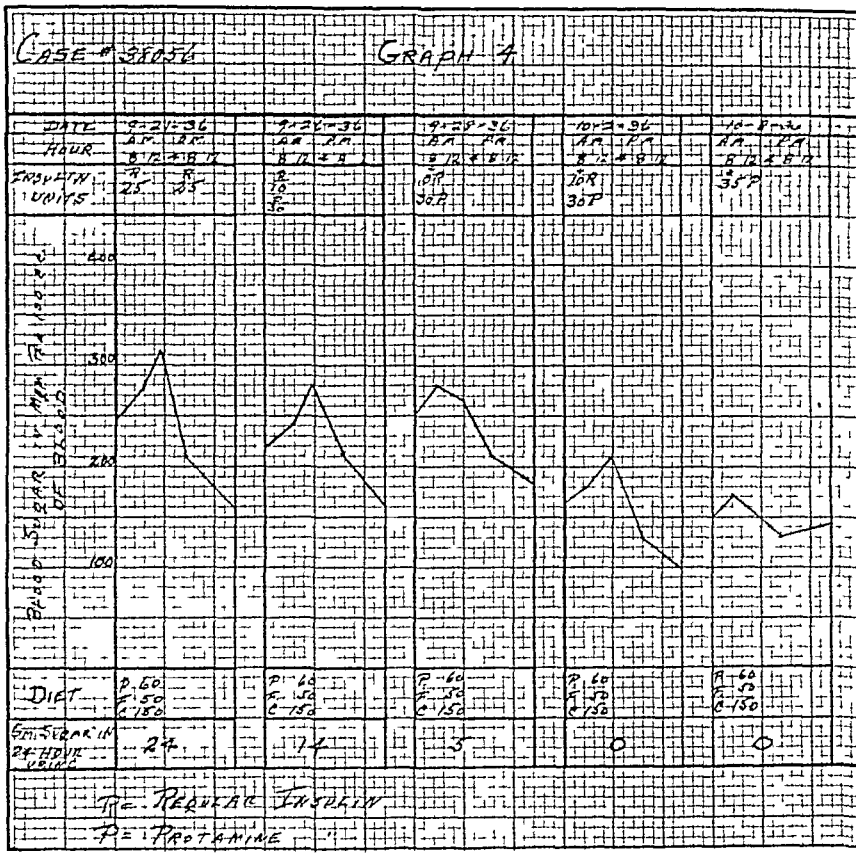


Case 3 (Graph 3) shows a moderately severe diabetes complicated by an attack of hyperthyroidism, with the control of the hyperthyroidism by thyroidectomy, marked fluctuation in the blood sugar persisted, and the usual dose of regular insulin proved inadequate. Instead of decreasing the diet which would have been distinctly harmful to the patient, we decided to replace some of the regular insulin with the protamine. This was carried out by giving the larger dose of regular insulin at 8 a.m. and the smaller dose of protamine insulin as the 6 p.m. dose. The improvement in the sugar tolerance was so excellent after a period of this regime that the dosage was eventually reduced to 15 units of regular insulin in the morning and 20 units of protamine insulin at night with complete control of the diabetes. This case follows the procedure originally advocated by Hagedorn and his associates.

always remember that when protamine insulin is used, the calculations that are made are in reality operable over a period of seventy-two hours. Changes in the dose of protamine are not reflected in the blood sugar, or the morning urine, on the day the change is made. For this reason, one must expect some glycosuria for the first few days after the commencement of the protamine insulin therapy.

Several methods of procedure have been followed by different groups of investigators in regard to the amount and time of administration of the protamine insulin and it is my purpose to mention these methods and show their action by means of case illustrations. (1) The method employed by the original investigators consists of giving a dose of regular insulin at 8 a.m. and protamine at 6 p.m. The a.m. dose of regular insulin is about twice that of the p.m. dose of protamine insulin. Blood sugar determinations are made at 7-11-2-5-10, the micro method of Folin (3) being used for this purpose. Daily qualitative tests for urine sugar are made at intervals of two to three hours from 6:30 a.m. to 9:30 p.m. and the ammonia content of the urine determined for the twenty-four period as an indication of fluctuations in the acidosis. The total amount of insulin used during the twenty-four period is increased or decreased as clinical and laboratory indications arise. (2) The method of giving protamine insulin in the morning and regular insulin in the evening. (3) Regular insulin before breakfast and supper and protamine at bed time (10 p.m.). (4) The method of giving both doses as protamine insulin, one at 8 a.m. and one at 8 p.m. (5) The method of using one dose of protamine insulin in the morning, supplemented by a dose of regular insulin administered at the same time but at a different site of injection.

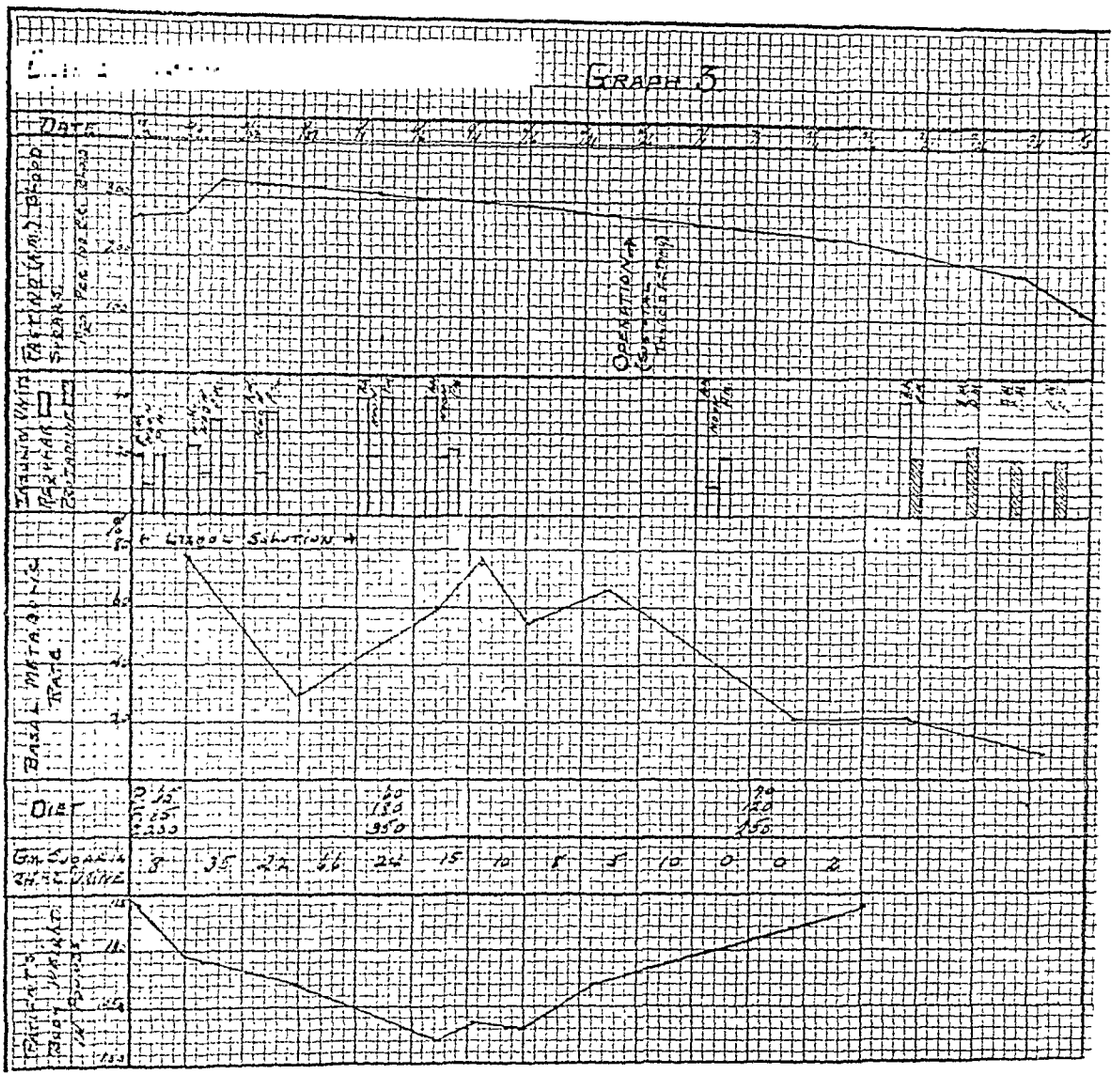
We have had fairly good results with the following procedure and I shall attempt to outline this in as practical a way as possible. We allow a dosage of protamine insulin equivalent to about seventy per cent of the calculated regular insulin requirement that has been given to the particular case at the time. This is administered as one dose about one hour before breakfast. For the first four to seven days of this change from the regular insulin to the protamine insulin, an



Case 4 (Graph 4) represents the procedure which we feel is most ideal for employment in making changes from regular to protamine insulin therapy. The number of injections is eventually reduced to one during the twenty-four hour period and the hyperglycemia and glycosuria kept under better control.

additional dose of the regular insulin equivalent to the remaining thirty per cent of the original insulin intake, is also given an hour before breakfast, using a separate syringe and a different site of injection. If after this four to seven day period, the morning urine fails to show sugar the regular insulin is discontinued. If hypoglycemic reactions have occurred during the night or in the early morning, the dose of the protamine is too large and should be reduced. If, on the other hand, sugar continues to be present in the morning urine, either the dose of the protamine insulin should be increased or the administration of the supplemental dose of regular insulin should be continued. The rate of increase or decrease of protamine insulin should never be more than five units at a time. It is also advisable, whenever possible, to do several blood sugars during the day especially before each meal, in order to have a fairly good idea as to the glycemic response to the treatment. If the proper dose cannot be arrived at to control the morning glycosuria without precipitating hypoglycemic reactions, then the small supplemental dose of regular insulin should be given over a longer period of time instead of increasing the dose of protamine. Emphasis must again be made that this dose of regular insulin is made as a separate injection, otherwise it will be precipitated by the mono-protamine and increase the effect of the protamine insulin.

Factors Influencing the Blood Sugar Level. It must be emphasized at this point that in all cases that fail to respond favorably to regular insulin therapy, a thorough search must be made to attempt to determine whether there are any additional factors responsible for the difficulty. I am, particularly stressing this point at this part of my presentation, for these same factors may act in exactly the same way with protamine insulin, perhaps in an even more exaggerated form and eventually lead to confusion and unwarranted discrediting of this preparation. First: An accurate consideration of the amount of physical and nervous energy expended by the patient is of utmost importance. It is not an uncommon experience to the careful observer to meet a case of diabetes which shows glycosuria when completely at rest and hypoglycemia on another day when the patient is especially active physically. Likewise the effect of nervous strain may produce similar results. In other words proper allowance should be made for additional physical or nervous expenditures of energy in the diabetic patient either by increasing the caloric intake for that period of additional activity or by reducing the amount of insulin allowed. This fundamental fact is very often lost sight of and may cause



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about 18 to 20 Gm. of sugar in the 24 hour urine specimen. The carbohydrate intake was then reduced from 250 Gm. to 200 Gm. with the same amount of insulin, without any evidence of checking the marked fluctuations in the blood sugar. It was then decided to use protamine insulin. His diet remained unchanged at P. 90 F. 100 C. 200 and he received protamine insulin 60 units at 8 a.m. and 20 units at 8 p.m. After four days of this regime, the blood sugar determinations before each meal had decreased to 52 mg., 125 mg. and 43 mg. and the urine negative. The following day the patient showed signs of insulin shock with a blood sugar of 34 mg. This was controlled without any difficulty. Inasmuch as the patient complained of being hungry most of the time on the diet allowed, it was decided to increase the diet rather than decrease the protamine insulin. Patient received P. 90 F. 120 C. 300 with 60 units of protamine at 8 a.m. and 20 units at 8 p.m. There were no marked fluctuations in the blood sugar noted any further and blood sugars before each meal on May 27 showed 129 mg., 166 mg. and 200 mg. respectively.

Case 2. (Graph 2). Patient was a 58 year old German sailor who developed a broncho-pneumonia, and in addition had a blood sugar of 235 mg. per 100 c.c. of blood and a CO_2 combining power of the blood plasma of 40 vol. % with 40 Gm. of sugar in the urine. The patient had been unaware of the existance of the diabetes. He was placed on a diet of P. 50 F. 50 C. 100 with regular insulin 30-10-30 (7/23/36). After four days a check revealed a fasting sugar of 234 mg. per 100 c.c. of blood with 5 Gm. of sugar in the urine. It was then decided to change the regular insulin administration to 40-20-20. After an additional seven days on this treatment the fasting blood sugar was still 222 mg. Another increase in the regular insulin was then made, so that patient was receiving 40-20-30 units and after a few days his urine became sugar free. It was then a question of increasing his diet and also of the convenience of this patient's receiving three injections of regular insulin a day after leaving the hospital. We felt that the use of protamine insulin might be of considerable help. The patient's diet was accordingly increased to P. 90 F. 60 C. 175 and protamine insulin given 40 units in a.m. and 20 units in p.m. After six days of this regime the patient reported that he felt exceptionally well, and his fasting blood sugar was 100 mg. with no sugar in the urine. The protamine insulin was accordingly reduced to 20 units in a.m. and 20 units in p.m. Thus this patient who on a diet of P. 75 F. 60 C. 120 and 90 units of regular insulin a day, still persisted in showing a considerable hyperglycemia, became normal with the use of only 40 units of protamine insulin a day, in spite of the fact that his diet was increased to P. 90 F. 60 C. 175.

Case 3. (Graph 3). This case is of particular interest as demonstrating the marked disturbance that can take place in the carbohydrate metabolism of a diabetic patient with the onset of hyperthyroidism. The patient was a 31 year old male with a diabetic history dating back twelve years. It is of interest to note that at that time I did a basal metabolism test and found it to be + 5%. Since that time the patient had been getting along on a fairly liberal diet with 20 units of regular insulin twice a day. Five months prior to the present admission to the hospital, patient began to complain of nervousness, palpitation, loss of weight and fatigue. His weight loss during the five months period was thirty-five pounds. On admission to the hospital his weight was 118 lbs. Fasting blood sugar 263 mg. per 100 c.c. of blood, and B. M. R. + 77%. He was given 5 minims of Lugol's solution three times a day and a diet of P. 90 F. 150 C. 250 with insulin 30-15-30. After ten days the B. M. R. dropped to + 30% but his weight had decreased further to 107 lbs. It was therefore decided to increase the caloric intake and also the amount of regular insulin, in order to stop the marked weight loss. Accordingly his diet was increased to P. 60 F. 180 C. 350 with regular insulin 40-20-25. In spite of this therapy the fasting blood sugar (6-3-36) remained elevated at 312 mg. and the weight showed a further decrease to 103½ lbs. His B. M. R. had risen to + 60% and his condition was considered very unfavorable. It was decided after considerable consultation, to attempt a subtotal thyroidectomy on the patient. This was performed on 6-25-36 and was effective in lowering the B. M. R. and eliminating most of the hyperthyroid symptoms. After a stormy convalescence, the control of the diabetes was again attempted. Accordingly, the patient was given a diet of P. 70 F. 120 C. 250 with regular insulin 40-10-20 units. The patient however continued to have a hyperglycemia (244 mg.) and glycosuria. Rather than decrease the diet or increase the dosage of regular insulin, we thought that protamine insulin should be tried. Accordingly the diet was kept the same and the morning dose of 40 units regular insulin was continued, and in addition 20 units protamine insulin allowed at 6 p.m. After two days the patient had an insulin reaction at 2 a.m. and as a result the insulin dosage was further reduced to 20 units regular in a.m. and 30 units protamine at 6 p.m. The patient continued to show marked improvement with absence of hyperglycemia or glycosuria, so that after ten days the insulin was further reduced to 20 units regular in a.m. and 20 units protamine at 6 p.m. The patient's weight had increased to 114 lbs. and he was sent home on the same caloric intake as above with 15 units regular insulin in a.m. and 20 units protamine insulin at night.

Case 4. (Graph 4). Patient was a 78 year old female with a history of diabetes of long standing. At the time of admission to the hospital she was suffering from a rather marked cardiac decompensation. In addition she complained of precordial pain with radiation down the left arm and weakness. The patient had not been receiving insulin prior to admission to the hospital. The blood sugar was 294 mg. per 100 c.c. of blood and CO_2 combining power of the blood plasma 49 vol. %. Her urinary sugar was 24 Gm. during the 24 hours. A diet consisting of P. 60 F. 50 C. 150 was allowed at time of admission with regular insulin Units 25-0-15. After a period of about 10 days (9-21-35) her blood sugar values before each meal were 271 mg., 308 mg. and 228 mg. with sugar excretion reduced to 14 Gm. for the twenty-four hour period. It was then decided to institute protamine insulin therapy rather than increase the regular insulin dosage, or decrease the carbohydrate content of the diet. Accordingly she received 30 units protamine insulin, and 10 units of regular insulin, one hour before breakfast, as separate injections. It is very interesting to note the gradual lowering of the sugar curves done at several day intervals, while on this regime. The last one performed was after the patient had been taking only the protamine insulin as one dose in the morning. Comparison of these different sugar curves shows the striking changes and resultant establishment of the blood sugar on a much lower level and without wide fluctuations during the twenty-four hour period.

DISCUSSION

The treatment of diabetes with protamine insulin opens up new fields of possibilities. With the use of regular insulin the moderate case offers little difficulty. The more severe forms of this disease however often show marked fluctuations in the blood sugar that cannot be controlled without either reducing the carbohydrate intake or administering insulin at more frequent intervals. Because of its prolonged action protamine insulin becomes ideally suited for treating such cases. In doing this one must avoid the error of changing too many factors at any one time or of making too frequent changes. This point cannot be stressed too much.

Thus, when the change is made from regular to protamine insulin, the dietary factor should not be changed at the same time. Likewise a sufficient period must be allowed for observing the effects of this change before attempting additional ones. From a practical point of view it is much better to begin with too small a dose of protamine insulin rather than a too large one. A fairly good idea is usually obtained as to the course of the blood sugar, if three determinations are made, one before each meal about every fourth or fifth day, and the urine examined at varying periods after each of these meals.

SUMMARY

1. Diabetes showing marked fluctuations in the blood sugar, or those cases associated with certain complicating factors, as hyperthyroidism, hepatic enlargement, etc., can be controlled better by protamine insulin than by regular insulin.

2. Cases of diabetes showing a persistent hyperglycemia or where it is desired to diminish the frequency of insulin administration should receive protamine insulin.

3. Protamine insulin should not be used in cases of acidosis or impending coma or those complicated by surgical conditions.

4. Untreated cases of diabetes should not receive protamine insulin as an initial form of treatment.

5. When changing from regular to protamine insulin we have obtained good results by giving 70% of this amount as protamine insulin and the balance as regular insulin, both administered about one hour before breakfast as separate injections.

6. After a period of 4 to 7 days if the morning urine is sugar free, discontinue the dose of regular insulin. If the morning glycosuria persists, increase the protamine insulin.

7. Increases or decreases in protamine insulin should consist of only five units at a time.

8. Too many factors should not be changed at one time, nor should the effected changes be made at too frequent intervals, when using protamine insulin.

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The Present Evaluation of Vitamin B_1 Therapy*

By

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THIS paper will attempt to evaluate the therapeutic importance of vitamin B_1 up to the present time. By emphasizing the word "present" we come face to face with the fact that we are about to discuss a subject which is still vague, still in the process of emerging from an experimental problem to an accepted clinical concept.

After years of investigation, vitamin B_1 has finally yielded its precise chemical structure and molecular arrangement (1) and, within the past two months, its artificial synthesis has become an accomplished fact (2). The biochemist has made this vitamin available (3) and we, as clinicians, must be prepared to use it with an understanding of its clinical indications and its limitations.

Three questions present themselves:

1. What is the state of vitamin B_1 deficiency in humans?

2. What is the action of vitamin B_1 in the presence of this deficiency? and

3. Why should we use vitamin B_1, clinically, in diseases other than proven B_1 avitaminosis?

We are all familiar with the fact that *beriberi* is due to a vitamin B_1 deficiency. As a matter of fact, it represents a stage of deficiency so marked that death will invariably occur unless large amounts of vitamin B_1 are given. Thus it has been shown, that in severe cases of beriberi, the administration of vitamin B_1 by mouth is often insufficient to prevent death (4). In these cases, intravenous injections are necessary since gastro-intestinal disturbances interfere with adequate vitamin absorption. This is well known to the workers in the Orient, particularly to those who deal with the problem of infantile beriberi (5). It may not be familiar to all in this audience that the second most frequent cause of infant mortality in China, the Philippines and adjacent countries, is infantile beriberi. The vast majority of these infants are borne of beriberi mothers (6). The method of treatment of infantile beriberi has become fairly well standardized. Even before crystalline vitamin B_1 was available, a concentrate of sufficient potency for intramuscular injection was widely used throughout the Orient. The concentrate is known as "tiki-tiki" and in severe cases of infantile beriberi it is given by subcutaneous or intramuscular injections of 1 c.c. every hour for six, eight or even twelve doses. As soon as the response takes place, which usually occurs within a few hours, the infant stops vomiting, there is cessation of convulsions and fluids are retained. Vitamin B_1 is then continued by oral administration.

As well known as beriberi is in the East, just so rarely do we see it here and the diagnosis of a proven case of beriberi merits a report in one of our medical journals (7). In the East, workers in this field also recognize a clinical entity which they describe as

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latent or sub-clinical beriberi. By that is meant a state of vitamin B_1 deficiency which is not severe enough to give the classical symptoms of beriberi but which, nevertheless, has a fairly well recognized set of symptoms interfering with normal health. If allowed to continue for a sufficient length of time, true beriberi develops. This state of ill health, the sub-clinical phase of the disease, entirely disappears with administration of vitamin B_1 for a sufficient period of time.

Now, then, if we here in this country were to confine our use of vitamin B_1 to those cases in which its deficiency was sufficiently well marked to be readily recognizable, there would be no point to this paper. This brings us to the third hypothetical question: why should we consider the therapeutic administration of vitamin B_1 in conditions other than proven B_1 avitaminosis. Of course, the answer to this question is based upon the hypothetical assumption that there are states of partial vitamin B_1 deficiency too mild or too recent to be detected as definite entities (8).

In our early work, the problem was to determine how these states could be recognized. No clinical sign, no laboratory test was available so we fell back on the method of trial and error. Through funds furnished by the Carnegie Institution of Washington, D. C., a large amount of crystalline vitamin B_1 was prepared by my chemical associates and with crystalline vitamin B_1 as the only therapeutic agent, we began the study of a controlled series of chosen cases.

Since *polyneuritis* is so typical of true as well as latent beriberi, we studied this group first. All types of neuritis were included in the study group. To date, over two hundred and fifty cases have been followed with varying degrees of improvement; i. e. from partial relief of pain to complete disappearance of all symptoms; in about 90% of cases.

Our results have been substantiated by a number of other investigators (9, 10, 11, 12). Speaking conservatively, then, we can say that vitamin B_1 is an important therapeutic agent in the treatment of neuritis. You will notice that I have not defined the word neuritis and I have done that deliberately, because the results of vitamin B_1 administration are equally good in localized neuritis as they are in polyneuritis; equally beneficial in neuritis of so-called alcoholic origin as in neuritis associated with infection, anemia, pregnancy or that due to other etiological agents. We see in the action of vitamin B_1 in neuritis, a real analogy to the action of iron in all types of secondary anemia. In alcoholic neuritis we can, by the administration of adequate amounts of vitamin B_1, bring about marked improvement or complete disappearance of all symptoms even though there is no change in the alcohol consumption. Careful study of these patients, however, indicates that the alcohol probably does not play a direct part in the production of the neuritis but that these individuals have really been on a vitamin B_1 deficient diet. If these patients continue to ingest an adequate amount of vitamin B_1, there will be no recurrence of their neuritis. In all of these cases, the duration of the symptoms bears a direct relationship to the duration of treatment. Polyneuritis that has been present for from three to six months, will subside after a few weeks of treatment. Polyneuritis of ten or more years' duration may, in a very short period of time, reach a state of marked improvement but complete disappearance of symptoms may not take place even after three or four months of treatment. This is equally true in experimental animals in which two stages of B_1 deficiency—an acute and a chronic stage—are observed (13). The acute stage will disappear quickly and completely on vitamin B_1 and post mortem studies of these cured animals show little or no cellular changes. The chronic stage responds slowly and gradually. Even after the animals appeared cured, clinically, and then were sacrificed, it was possible to demonstrate many types of cellular change in central nervous system and peripheral nerves, varying somewhat for the different species of animal used (14).

The value of vitamin B_1 in *pregnancy* has an important practical significance. The view that pregnancy induces a deficiency state has been expressed by many investigators (15). The occurrence of anemia, the diminution or absence of gastric acidity, the demineralization, the polyneuritis and, perhaps, even the toxemias, all point to a deficiency state. When neuritis occurs in pregnancy, the ingestion of vitamin B_1 is followed by a marked improvement or disappearance of the polyneuritic manifestations (16, 17, 18).

From the clinical point of view, the group of neuritis most often seen are the so-called sciatic, the sacro-iliac and the shoulder girdle neuritides. These cases are frequently associated with areas of focal infection and, as a matter of fact, we have all seen, in occasional patients, a dramatic improvement following the removal of a correlated infected area. Unfortunately, such cures are few in number as compared with the disappointments that have followed the removal of teeth, tonsillectomy and similar procedures. A number of cases in our series have fallen directly into this group and we have attempted to evaluate the benefit from vitamin B_1 therapy regardless of the continued existence of a proven focus of infection. In this group, also, there has been a marked improvement in a large number of cases. It must be freely admitted, however, that there is a considerable proportion of recurrences in these cases of infectious neuritis—recurrences which, apparently, are due to the constant absorption of bacterial toxins. It is not surprising that such a condition prevails in this group. It is surprising, rather, that in the presence of a focus of infection, as marked an improvement as 70% could be noted.

The groups mentioned already are those most frequently observed in clinical practice but there are many others that merit consideration. The first to be included are the cases of neuritis *associated with varying types of anemia* of which, perhaps, the most interesting is the group associated with primary macrocytic anemias. The improvement in the neuritic manifestations of macrocytic anemia has been observed by other investigators as well as ourselves. There is a special problem connected with this group —the problem of dosage and duration of treatment. It seems possible that the clinical paradox of the pernicious anemia patient showing improvement in his blood picture but dying of subacute combined degeneration of the cord may be modified by vitamin B_1 therapy. Further studies are necessary in these cases. Certainly, neuritis associated with secondary anemia usually responds readily.

Among the less common types of neuritis are those associated with *lead poisoning* and other heavy metals and here attention is directed to the arsenical neuritis

occurring during intensive treatment for syphilis. These types of neuritis have been included among our series and show a gratifying response to the use of vitamin B_1 therapy.

We have had the opportunity to study five cases of severe trigeminal neuritis—the so-called *tic douloureux*—all of whom were operated upon and showed recurrences post-operatively. Three of these five have now had complete relief of symptoms; the other two are showing improvement while still taking vitamin B_1.

Recent experiences with *optic neuritis* and auditory neuritis are of interest. Our own series consists of too small and too recent a group to warrant positive statements but some good results have been reported already to me, personally. These two groups offer a very fruitful field for the specialists in these branches of medicine.

We must then summarize our experience in the treatment of all forms of neuritis by vitamin B_1 as one that justifies its use by giving a large percentage of improvement or cessation of symptoms. I want to call to your attention the fact that in practically none of these cases was it possible to say, at the beginning of treatment, that a vitamin B_1 deficiency state surely existed. The value of vitamin B_1 therapy in neuritis is emphasized again and again because, up to the present time, there is no other syndrome in clinical medicine in which we are as sure of its worth except, of course, in true or latent beriberi.

Herpes zoster belongs among the neuropathies frequently seen in clinical practice. The experimental physiologist has studied the possible relationship of vitamin B_1 to the susceptibility of experimental animals to the virus of herpes (19). At the present time, results are inconclusive. We have had the opportunity to study the effect of vitamin B_1 in its relation to the post-herpetic paresthesias and anesthesias and our clinical results suggest a definite beneficial action, namely, a quicker disappearance of the residual symptoms, and a smaller number of cases with persistent anesthesia in the treated cases than in the controlled series.

A recent report in the German literature describes the value of vitamin B complex in the treatment of *mild chorea* (20). We have had no experience with this type of case but I mention it as it is of interest to men in pediatric practice.

Now, we must leave what is fairly well proven and go on to the more hypothetical and, therefore, questionable use of vitamin B_1. Experimentally, in animals, there is a definite relationship between vitamin B_1 and the carbohydrate metabolism. The relationship is a complex one but a careful survey of the vast biochemical studies gives the following data:

1. In dogs, deprivation of vitamin B_1 is followed by an increased blood sugar and the presence of urinary sugar (21). When insulin is given to these animals, the blood sugar level decreases and the urinary sugar disappears but in spite of insulin, the animals go on to death. Careful studies of the blood chemistry of these animals show no significant changes in the nitrogen elements but the carbon dioxide of the blood falls and the lactic acid level increases (22).

2. The rate at which the symptoms and signs of vitamin B_1 deficiency develops in all animals can be influenced by the amount of carbohydrate in the diet, i. e., the larger the amount of carbohydrate ingested the more rapid is the onset of the manifestations of avitaminosis. Death occurs more rapidly in animals on a high carbohydrate diet than in those on a low carbohydrate diet (23).

3. The change in the carbohydrate metabolism in B_1 avitaminosis is a cellular one and has been demonstrated in minced tissue outside of the body. The brains of B_1 deficient pigeons, in vitro, show a lower capacity to take up oxygen than normal pigeons brains (24). In the avitaminotic brain tissue is found increased lactic acid and pyruvic acid. The latter is not found in the normals (25). By adding crystalline vitamin B_1 to the minced avitaminotic brain tissue, the oxygen take up approaches the normal, the lactic acid decreases and the pyruvic acid disappears (26, 27, 28). The ratio between increased oxygen take up and pyruvic acid disappearing was a fixed constant. Recently, increased pyruvic acid was found in the blood of avitaminotic pigeons and rats in large amounts (29). This returns towards normal in animals cured by the administration of vitamin B_1 (30).

So close, then, is this relationship between vitamin B_1 and carbohydrate metabolism, that the state of B_1 deficiency has been referred to as "a chronic carbohydrate poisoning" (31).

In our clinical experiments, we have been studying the effect of vitamin B_1 in cases of known *carbohydrate disturbances* of all degrees and severity (32). Into this group fell cases that were classified as diabetes. In the majority of cases of true diabetes mellitus, we have seen no beneficial effect from the administration of vitamin B_1. I would like to make this more emphatic by stating that we have actually seen an increase in blood sugar and urinary sugar output in some of these patients; so that the question of whether vitamin B_1 brought on an aggravation of the diabetic state may justly be raised. However, a few of our cases showed a startling modification of the carbohydrate disturbance with lowered blood sugars and lowered urinary sugar output. In those patients with disturbance of the carbohydrate metabolism in whom other stigmata of deficiency co-exist such as unexplained obesity, the loss of appetite, polyneuritic manifestations and diminished metabolic rates, we have obtained our best results. These patients fell into the group described by Joslin as "unclassified diabetes." Careful analysis of the marked change in their carbohydrate metabolism after taking vitamin B_1 raises considerable doubt as to whether these patients belong in any diabetic grouping.

It has been proven, experimentally, that vitamin B_1 is of fundamental importance in the carbohydrate metabolism. The confusion as to its clinical use is due to our clinical inability to separate true diabetes mellitus from the other forms. It seems likely that among these other forms are cases of partial vitamin B_1 avitaminosis which is reflected in the carbohydrate disturbance. These cannot, as yet, be separated but chemical studies now under investigation offer the prospect of a solution to this problem. Until these false diabetics can be recognized easily, the use of vitamin B_1 in so-called clinical diabetes is justified only on an experimental basis (33, 34, 35).

Another interesting relationship is that of vitamin B_1 to *metabolism* (36). In dogs on a B_1 deficient diet, the time required for the development of anorexia is

an accurate indication of the rate at which avitaminosis is developing. By forced exercise the time required for anorexia to appear is materially shortened (37). When thyroid is administered to induce hyperthyroidism in these dogs, anorexia develops very rapidly (38). Experiments on pigeons also show a greater vitamin B_1 requirement in hyperthyroidism than under normal conditions (39). In rats, protection against thyroxin poisoning can be accomplished by the administration of vitamin B_1 (40).

It is a justifiable conclusion from these and other studies that the vitamin B_1 requirement of an animal is proportionate to the metabolism of the animal (41). Some recent studies with dinitrophenol show that this drug does not influence the B_1 requirement of the animal but that "the total caloric intake and body weight are the most important factors in determining the vitamin B_1 requirement of the organism (42)."

With this experimental background, we have included for clinical study a group of cases ordinarily classified as *hypothyroidism*. These have a lowered *metabolic rate, usually not lower than minus twenty-four*, a moderate obesity and, yet, show none of the mental stigmata of true hypothyroidism. In several of these patients under observation, the administration of thyroid has been of little or no value. They appear to be cases of lowered general metabolism rather than of thyroid deficiency. The action of vitamin B_1 in these cases is the action of a metabolic stimulant. We are, at present, studying more of these cases and have observed improvement not only in the clinical state but a return of the basal metabolic figures to the normal. Detailed studies of this group will be reported in another paper.

I should like very much to close the discussion of vitamin B_1 therapy at this point but I would be omitting a group of cases in which vitamin B_1, apparently, has some value. These patients complain of *vague gastro-intestinal disturbances* (43) associated with constipation and show unexplained gastro-intestinal hypotonia on X-ray examination. I should like to omit this group of cases because in the literature of pharmaceutical houses this vague syndrome has been over-exploited and over-emphasized. The failure to improve many cases of infantile and adult constipation with the use of vitamin B_1 has served to discredit the value of this important therapeutic agent. Vitamin B_1, as I have said before, is not a constipation cure. There are, unquestionably, some patients in whom constipation results from a vitamin B_1 deficiency state (44) but they represent an extremely small percentage of cases. If vitamin B_1 is to be judged as a therapeutic agent on its response in cases of unexplained constipation, the results are bound to be disappointing.

Up to this point, I have attempted to confine the discussion of the value of vitamin B_1 to fairly well established clinical states. In addition to those states described, there are some obscure and ill-defined clinical entities, characterized usually by one symptom or another, in which vitamin B_1 is indicated but here again a word of caution as to its value must be expressed. I refer particularly to those cases of loss of appetite. Much has been published about the tremendous value of vitamin B_1 in anorexia. It is true that experimentally induced vitamin B_1 deficiency in animals is characterized by a marked loss of appetite. It is also recognized that by feeding vitamin B_1 the appetite promptly returns. This occurs in patients who have a similar deficiency state. However, it is unwise to use as a clinical yardstick the existence of anorexia to justify a prescription for vitamin B_1. This is especially true in children where *anorexia* is too often the result of a psychological problem at home, a behavior characteristic rather than a vitamin B_1 deficiency state. The value of vitamin B_1 in stimulating appetite finds its greater usefulness in the anorexia associated with long standing illnesses or in patients on limited diets for various chronic diseases, and obesity. In such patients the disappearance of anorexia is frequently observed. The next poorly defined state that we will consider for a moment is that characterized by unexplained weakness, and again the same rule applies that has been expressed in relation to loss of appetite. Unexplained weakness is, too often, an early symptom of an early or obscure organic diseased state or, at times, particularly in adults, too often an expression of psychological maladjustment. To expect that the administration of vitamin B_1 will be followed by a return of vigor and energy in many of these patients is to believe in the impossible. Just as in loss of appetite, weakness following convalescence from a serious illness or associated with long continued malnutrition will often disappear with the administration of vitamin B_1.

Throughout this paper, I have repeatedly used two phrases

(1) "adequate amounts of vitamin B_1"; and
(2) "for a long enough period of time"

and I feel that I have come to the point where these phrases must be more explicitly defined. There are available, at the present time, to the physician, many different sources of vitamin B_1. The crystalline material which is made by Merck & Company is available only in small amounts. It is difficult to procure and it is expensive. At the present time, its use should be reserved for those severe cases of vitamin B_1 deficiency that require a large dose in a short period of time and for those cases in which vomiting, diarrhea or extensive gastro-intestinal disease preclude the probability that there will be adequate absorption of vitamin B_1 if given by mouth. In such cases, the administration of from two to ten mgm. as a daily dose may be desirable. In advanced B_1 avitaminosis where the question of death is a pressing possibility, the administration of ten mgm., intravenously, once a day, may be safely used. Within five days, or sooner, an improvement will be noted if the diagnosis of a vitamin B_1 deficiency is correct.

However, such cases represent a very small percentage of those under consideration. For all the rest, vitamin B_1 by mouth will suffice. Here the crystalline product need not be employed, as sufficiently strong vitamin B_1 concentrates are available. The factor of dosage must be determined on the basis of units of vitamin activity. Unfortunately, there is some confusion at present, as two standards are in general use, the first being the Sherman Chase unit and the second being the International unit. 1.3 Sherman Chase units is the equivalent of 1 International unit. In the majority of cases of adults, it is desirable to administer from one to two thousand Sherman Chase units a day. Therefore, it becomes necessary to determine the Sherman Chase unit content of the preparation to be used and I am happy to say that through the cooperation of many of the pharmaceutical houses, the recent

products are all labelled with their vitamin unit content. Preparations in capsule form, containing from two to four hundred units per capsule are available and, thus, by the administration of from three to six capsules a day, an adequate amount of vitamin B_1 can be administered readily. Most of the concentrates on the market contain sizeable amounts of vitamin B_2 and vitamin B_4. It should be emphasized, at this point, that in our first hundred cases the results were obtained with crystalline material in which, therefore, we were certain that we were only using vitamin B_1. In the subsequent larger number of cases now under consideration, we have used the cheaper commercial concentrates and in the same dosage we have not observed any difference in our results, so that the amounts of vitamin B_2 and vitamin B_4 in the preparations that will be widely used, because of their availability and because of their lowered cost, do not seem to play a significant role in the therapeutic results.

The next factor of importance, as we have stressed it again and again in this paper, is the duration of time. How long should a patient take two thousand Sherman Chase units of vitamin B_1 a day before he may expect a result? This is a question which is very important to the physician as well as to the patient. In the light of our present knowledge, we are well aware of some of the factors that complicate this problem. The first, of course, is the duration of the symptoms or the duration of the disease process and, as I have indicated before, a polyneuritis of two or three months duration will respond in a short period of time, usually in three or four weeks. A polyneuritis of five to ten years' duration may not begin to show response for three or four weeks and response may not be marked until twelve or more weeks of treatment. This is frequently so in those cases of disturbance of the carbohydrate metabolism and, in fact, in cases of general lowered metabolism to which I have referred. In such, some improvement is usually noted in four weeks. In our series of cases, if an improvement was not observed in four weeks, it did not occur at all and such a patient would probably not be benefited by continued use of vitamin B_1 for a longer period of time. This is especially true in cases of unexplained anorexia and unexplained weakness. If a vitamin B_1 deficiency is responsible for the loss of appetite or weakness, a response usually occurs within two weeks of treatment on two thousand Sherman Chase units a day, and if after four weeks there has been no improvement, the failure to modify the symptoms is usually a very reliable indication of an inaccurate diagnosis and an inaccurate indication for the use of vitamin B_1 in that particular patient.

There are several other factors that modify the duration of treatment. Experiments have shown that metabolism influences the vitamin B_1 requirement—that in an artifically induced hyperthyroidism, the vitamin B_1 requirement is greater; that in animals on forced exercise, there is also an increase in the need for vitamin B_1 in the tissues. These experiments are useful guides in the interpretation of the problem of how long to give vitamin B_1. In those cases of pregnancy in which it is of use, it is to be given during the entire term of pregnancy. The vitamin B_1 content of the new born infant is directly related to the amount of vitamin B_1 available in the pregnant mother. In this regard, the new born infant responds to vitamin B_1 deprivation and to vitamin B_1 administration in the same way as it does to the deprivation or administration of the hematopoietic substances in the pregnant mother. The analogy is carried further, since vitamin B_1 in excess of the needs of the patient is excreted in the urine (45) as, you will recall, has been demonstrated in the case of the anti-anemic principle (46). Experimentally, it is possible to cure rats and other animals by feeding them human urine from individuals receiving an adequate amount of vitamin B_1 in their diet (47, 48), just as in the same manner it has been possible to effect reticulocytosis by the rectal administration of human urine from normal individuals (49). Large amounts of urine from patients suffering from beriberi have no effect upon the course of vitamin B_1 deficiency in rats.

An interesting observation on the use of vitamin B_1 should be noted at this point. About 20% of all cases of polyneuritis experience an intensification or aggravation of their neuritic pain soon after starting oral treatment. The increased pain is usually noticed in from three to five days from the onset of treatment and is most intense about the seventh day. Thereafter, the pains subside and improvement takes place. The reason for this acute temporary exacerbation is not clear, but it occurs often enough to justify a warning of its occurrence to the patient who is about to commence treatment.

There is, at least, one more question that must be answered before closing and that is, what are the contraindications to the administration of vitamin B_1? Is there such a thing as an overdose—a hypervitaminosis? This question was one of the first that we investigated in our experiments with humans. We administered as high as ninety thousand Sherman Chase units a day to some patients and were unable to observe any harmful effect. We were able to detect large amounts of vitamin B_1 in the urine of individuals on excessive dosage and this seems to be the factor of safety. Similarly, we have had patients who have taken vitamin B_1 daily in dosage of from one to two thousand Sherman Chase units a day, for over two years and we have not observed any untoward effects. The lessons learned from biochemical and physiological experiments with this vitamin indicate that this is what we should expect. Storage of vitamin B_1 within the body has not been demonstrated and it probably does not exist. The action of vitamin B_1 is the action of a catalyst that concerns itself with oxidation of the degradation products of glucolysis.

In vitamin B_1 we have in our hands an important therapeutic substance whose usefulness has not been thoroughly defined. At the present time, we must take the greatest care to confine its clinical use to those entities described in this paper. If we attempt to use it indiscriminately, we shall bring discredit upon it. If the dosage used is inadequate or if its administration is for too short a period of time, many patients will be deprived of benefit which would otherwise be theirs. The full scope of its usefulness has not yet been determined. Many clinical experiments are in progress. More and more reports are appearing in the world literature. I have no hesitancy in prophesying that we shall hear much more about the therapeutic value of vitamin B_1 in the next few years.

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SECTION IV—*Roentgenology*

Large Diverticula of the Gastric Cardia*

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TRUE diverticula of the stomach are uncommon and although often symptomless may cause confusion with other types of lesion. Larimore and Graham (1) in a series of 3,446 gastro-intestinal X-ray examinations observed 105 diverticula, only three of which were in the stomach. We encountered only two instances of gastric diverticula in 11,828 examinations done at Stanford University Hospital over a twelve year period. Our two other cases were seen at other hospitals. The Mayo Clinic reports fourteen cases proven anatomically (2), six of which were at the cardia on the posterior wall. They had in all twenty-five cases diagnosed by roentgen ray (2 and 3), only two of which were proven, and four of which

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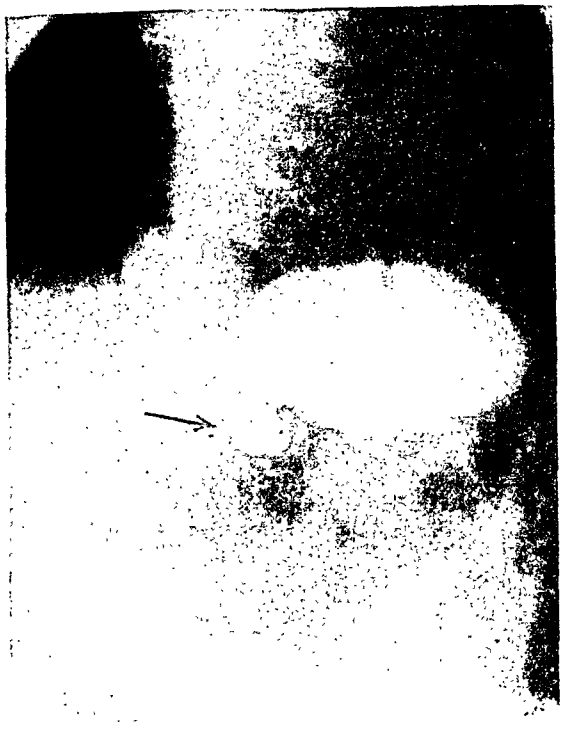


Fig. 1: Case 1. Diverticulum of the stomach at the cardia. Proved by operation.

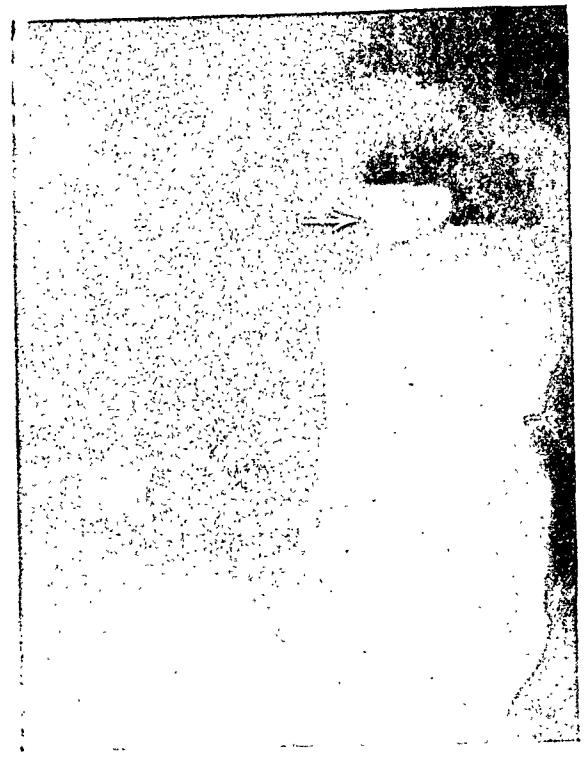


Fig. 3. Case 2. Diverticulum of the stomach at the cardia. This did not fill from the esophagus but only by reflux from the stomach. It was still full of barium after twenty-four hours.

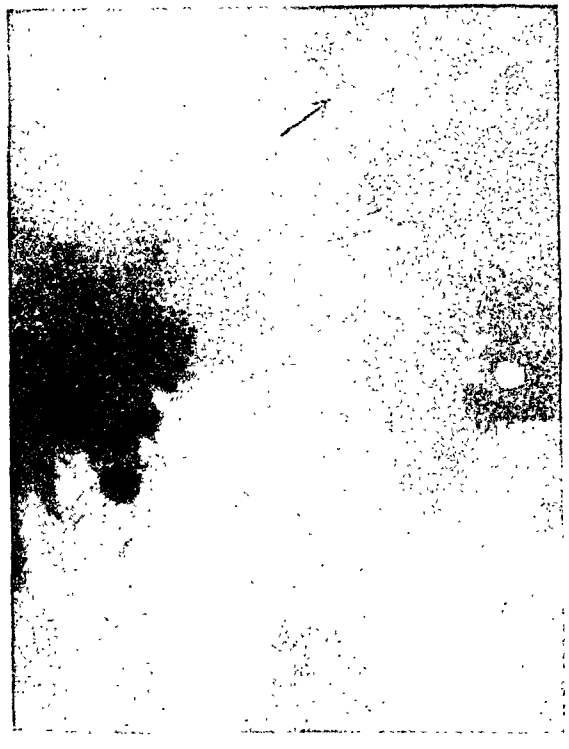


Fig. 2. Case 1. Residue in gastric diverticulum twenty-four hours after barium meal.

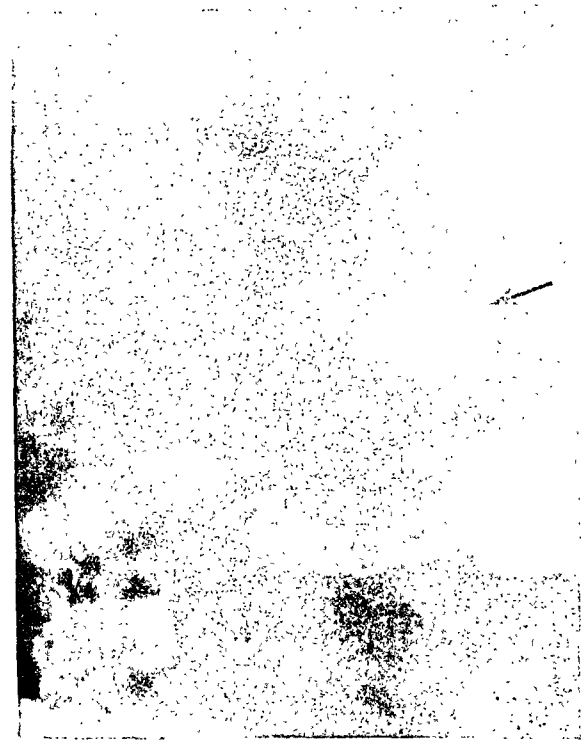


Fig. 4. Case 3. Diverticulum of the stomach at the cardia. It measured three and one-half centimeters in diameter.

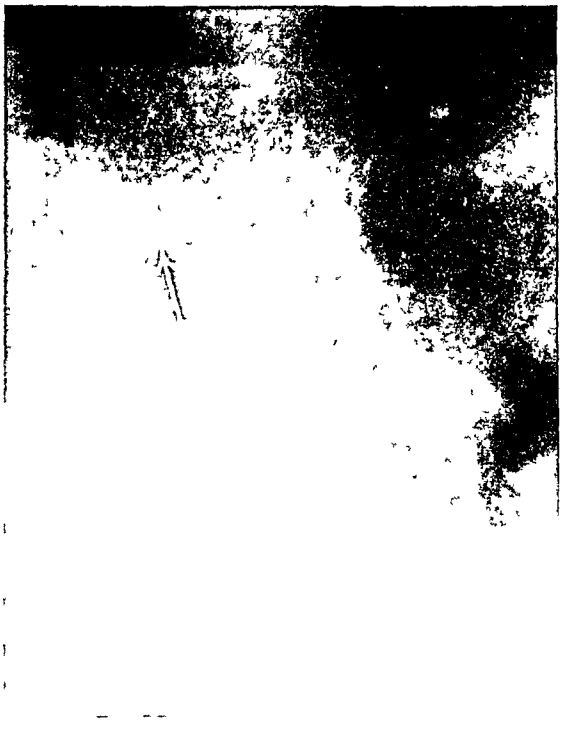


Fig. 5 Case 3. The diverticulum was still full four hours later. Attempts to hasten its emptying by putting patient on right or left side or even head down always were ineffective.

were shown actually to be something else. In 64% of their cases there were no symptoms attributable to the diverticula, and even in the other cases the origin of the patients' complaints was uncertain. Neoplasms and ulcers were found in or near the pouches in several instances, but only one case was complicated by hemorrhage. Most recently Martin (4) has collected data on 103 published cases of uncomplicated pulsion diverticula of the stomach, including five from the post mortem records of the Johns Hopkins Hospital. He was unable to find the record of a single case diagnosed, ante mortem, either clinically or by X-ray.

True primary diverticula are thought to be congenital in origin and are distinct pathologically from those due to extrinsic or intrinsic disease of the stomach wall. There are no characteristic symptoms upon which to base a diagnosis, consequently the X-ray examination is all-important, but it will not always reveal whether the diverticulum is a true or a false one.

We are reporting four examples of this rare gastric lesion. One patient was operated upon. The large size of the diverticula in the others makes the X-ray diagnosis reasonably certain.

Case 1 Miss F. H., age 20, complained of indefinitely-localized pain in the abdomen at times without relation to meals. Films of the gall bladder showed a calcified stone a centimeter in diameter. Barium meal revealed a pouch more than two centimeters in diameter on the lesser curvature of the stomach just below the cardia. This retained barium for at least twenty-four hours. Dr. Stillman removed the gall stone in January, 1926, but this operation failed to stop the pain. In August, 1926, he operated again and invaginated the diverticulum. He found no evidence of inflammation there. No biopsy was done to discover what coats were present in the wall of the pouch. The patient's pain was relieved.

Case 2. Mrs. E. V. C., a 62 year old widow entered the hospital December 2, 1929, complaining of indigestion. She had had irregular burning pains in the stomach unrelated to meals on and off for twenty years. Two years previously an X-ray diagnosis of duodenal ulcer was made and she has been on a modified Sippy regime since that time, but only with partial relief. *Physical examination* revealed moderate epigastric tenderness. The blood count was normal. The stool was negative for occult blood. The blood Wassermann was negative. Fractional gastric analysis after a histamine "test meal" showed small volumes of gastric secretion but a free acidity of 100° and a total acidity of 110°. A diverticulum of the stomach demonstrated by X-ray examination is illustrated in Fig. 3. No evidence of a duodenal ulcer was found. She was dismissed with a clinical diagnosis of psychoneurosis. She was known to be alive and well five and one-half years later.

Case 3. Mr. P. O., a 71 year old longshoreman, was in the hospital in 1929 for osteomyelitis of the big toe. In 1931 he entered again, his toe still sore, and complaining of occasional gastric distress and retching during the past month. He had had no severe pain and had not vomited. He used alcohol excessively at times.

In June, 1934, he entered again and has been under continuous observation since. During this time he has had four severe, acute abdominal attacks consisting of dull aching pains, burning, vomiting and abdominal distension. The abdomen is diffusely sore at the time of these episodes, but there is no localized tenderness. Each attack has followed a bout of heavy drinking. Blood has not been found in vomitus or stools, grossly or by chemical

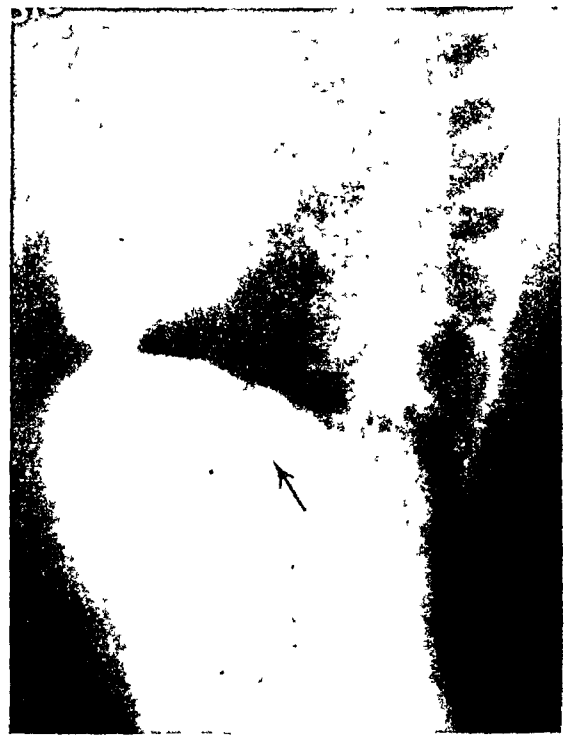


Fig. 6. Case 4. Diverticulum of the stomach near the cardia. (Lateral exposure).



Fig. 7. Case 4. Twenty-four hours after the barium meal, the gastric diverticulum is filled half with barium and half with air. (Antero-posterior exposure).

test. No leukocytosis was ever found. Gastric analysis after the injection of half a milligram of histamine, removing five samples at ten minute intervals, revealed a free HCl reaching 90° and a total acidity of 95°. All specimens contained excessive amounts of bile. A description of the gastric diverticulum found by X-ray examination accompanies Figs. 4 and 5. The patient is on a modified Sippy diet as he feels he has less indigestion than when following a regular diet. His substernal burning sensations are relieved by Sippy powders.

Case 4. Mrs. M. L. W., a 38 year old stenographer complained of lack of energy. She had two spontaneous miscarriages. Her appendix was removed in 1921 and a cystic ovary and one tube in 1923. Tonsillectomy was done in 1925 and curettage in 1928 and 1929. She had never been well since. She was weak, dizzy, faint and short of breath, and unable to do routine housework. She had no gastro-intestinal symptoms except moderate constipation.

On *physical examination* she appeared delicate. Both pupils showed congenital inferior coloboma. The blood pressure was 102/75. Old operative scars were present in the lower abdominal wall. Blood, urine and stool examinations were normal. Gastric analysis after an alcohol test meal revealed 6° of free HCl. The basal metabolism varied between plus five and minus eighteen. X-ray of the chest was negative. X-ray of the teeth revealed one area of periapical infection. The roentgen appearance of her gastric diverticulum is shown in Figs. 6 and 7.

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Volvulus of an Inverted Intrathoracic Stomach Complicating Diaphragmatic Hernia---Case Report

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THE history, symptoms, clinical and X-ray findings in this interesting case present in brief, a summary of the problems in differential diagnosis and complications of diaphragmatic hernia.

At one time or another, all of the abdominal viscera, except organs situated in the pelvis, have been found above the diaphragm in a hernia. (Richardson) (1). Of surgical importance are the stomach and colon, especially the transverse portion and the small intestines.

The first case of complete volvulus of the stomach was described by Berti in 1866. Berg in 1895 was the first to operate for gastric volvulus.

INCIDENCE OF VOLVULUS OF THE STOMACH

Payer (2) could find only 22 cases of volvulus of the stomach reported in the literature from 1866-1909 and quotes 500 cases of diaphragmatic hernia with 12 cases of gastric volvulus. Lahren (1927) summarized the literature reporting that there were then 40 known cases of gastric volvulus. Sutter (3) analyzed the 58 cases in the literature up to 1929. Sutter, however, excluded all cases which were due to diaphragmatic hernia. Deaver and Ashurst (4) (1921) state that volvulus of the stomach appears to have been observed in at least 35 cases, and that there are on record at least 22 operations for gastric volvulus. Anagnostidis (5) (1935) found reports of 116 cases of volvulus of the stomach.

Knaggs (6) (1904) reported 3 cases of volvulus of the stomach, complicating diaphragmatic hernia and remarks that strangulation affected that part of the stomach which had not entered the hernia; while the hernia contents themselves were quite normal. He explains that as due to interference with the circulation through the coronary vessels.

Submitted November 10, 1936.



Fig. 1. Real hydropneumothorax. Note: Heart not displaced, collapsed lung compressed against mediastinum, no lung tissue visible through gas-filled area.

All or only part of the stomach may be involved. The torsion may be: (1) around the axis from the pyloris to the cardia—the so-called organo-axial or pyloro-cardiac volvulus; (2) around the axis from the greater to the lesser curvature, the so-called mesenterico-axial volvulus, or (3) of a mixed type. In the series of 116 cases studied by Anagnostidis (5), the volvulus was described in detail in 108 and in 57 (52.7%) it was of the organo-axial type; in 45 (41.6%) of the mesenterico-axial type, and in 6 (5.5%) it was of the mixed type. In 43.9% of the 116 cases recorded in the literature the condition was described as idiopathic.

CASE HISTORY

H F, male, age 40, was seen for the first time on October 10, 1934, 1 A. M., for relief of what the patient termed as a "heart attack." The evening of the 10th, after partaking of a heavy meal, the patient began to complain of pain in the left chest, dyspnea and vomiting. On examination, a moderately obese middle-aged man appearing acutely ill with dyspnea, cyanosis, weak rapid pulse, profuse cold perspiration, and repeated projectile vomiting of foul brown fluid. The chest was barrel-shaped. No apical impulse was palpable in the left precordia. There was tympany in the left upper chest, with flatness in the left lower. There was dullness to the right of the sternum. Apex beat palpable 1 inch within right nipple line. Pulse 120, respiration 24, blood pressure 90/40. Distant breath sounds were heard in the left apex.

The dyspnea and cyanosis directed one's attention to the chest. The shock and vomiting to the abdomen. The abdomen was soft, flat, no masses or tenderness, no peristaltic waves. The displacement of the heart and percussion and auscultatory changes pointed to chest pathology.

On further questioning the following information was elicited: That he had recurrent attacks past 8 years. Last attack one month ago with pain in chest, dyspnea, and vomiting. Seen by physician who administered 2 hypodermics—patient felt better next day. Inquiring if any X-ray had been taken, the wife stated that he had been studied in a New York hospital, found to have an unusual condition—and that she had hidden the plates in her trunk. The X-rays were found and revealed a stomach within the thoracic cavity, hanging in an inverted position, also the presence of the large intestine in the thorax.

The vomiting, tympany of left chest and the presence of large intestines in the thorax made one suspicious of possible angulation or kinking of the herniated large gut. *But*—the absence of any abdominal distension was opposed to any obstruction or incarceration of the large bowel. The following morning patient felt somewhat better. That afternoon he started spilling over more brownish fluid. He was seen and found to have a fuller stronger pulse, dyspnea and cyanosis still present but not as marked, no pain. Pulse 100, temperature 97, respiration 20. The abdomen remained soft. The patient was reluctant to enter the hospital for observation since his previous attacks, he argued, were relieved without hospitalization. After persuasion he was admitted to the Cedars of Lebanon Hospital the evening of the 10th with a diagnosis of a partial volvulus of the stomach complicating diaphragmatic hernia.

On admission to the hospital, his temperature was 99.6, pulse 120, respiration 20. The following procedures were instituted: Levine tube was passed intranasally for continuous drainage of the stomach. 60 c.c. of brownish fluid were obtained. An intravenous glucose and saline 1000 c.c. was slowly given so as not to embarrass the heart. Rectal tube to relieve any gas in the large gut. Morphine and atrophine for pain. That evening patient was much more comfortable. Small amount of drainage was passing through Levine tube. Had a fairly good night. The following morning, 24 hours after admission, temperature rose to 101, pulse 115, respiration 28. Cyanosis was more marked, breathing more labored. Several hundred c.c. of gastric fluid drained through tube during the night. Changing the position of the patient increased the amount of fluid that could be withdrawn with the syringe attached to the Levine tube.

If one saw the patient propped up in bed with cyanosis of lips, face, fingernails, with a thready rapid pulse, marked dyspnea, and temperature rising to 103 one was sure it was pneumonia. The chest findings would confirm any number of diagnosis. The signs in the chest could not be interpreted in terms of either *normal* or *pathological thoracic* findings because the patient had abdominal viscera in the thoracic cavity. The patient was transferred on his bed to the X-ray room to observe what was happening within the chest. X-ray showed the Levine tube

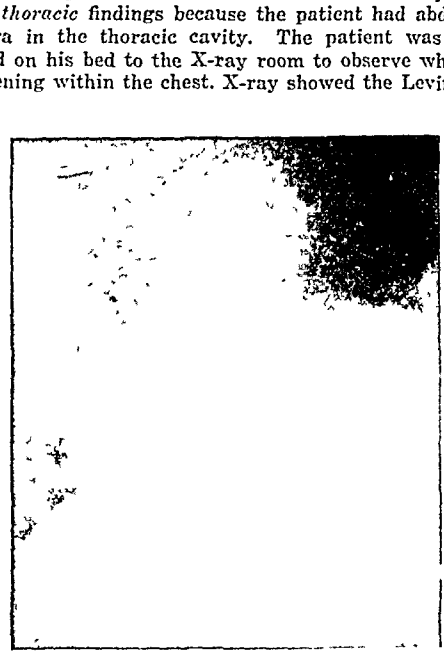


Fig. 2. X-ray of patient March 2, 1927. False hydropneumothorax. Note: Heart displaced to right, lung not collapsed, but surrounds gas-filled area, which occupies a central position. Some lung tissue can be seen through the gas. Stomach full.



Fig. 3. Same as Fig. 2 on fasting stomach. Note: No fluid level, large gas bubble.

in the esophagus, stomach greatly dilated, occupying most of the thoracic cavity (Fig. 8). Displacement of the heart to the extreme right. While the patient was being propped up for X-ray, the patient shook himself and a considerable flow of brownish fluid was noted escaping from the tube. Shaking the patient from side to side gave one the impression of shaking a half empty bottle of water. The fluid was sent to the laboratory for examination for blood and bile. If there was fluid trapped in the stomach, was it coming from obstruction below or at the stomach. IF bile was positive—the obstruction was beyond the duodenum. IF bile was absent—the obstruction was above the duodenum. The laboratory report was repeatedly negative for bile, but strongly positive for occult blood. White and differential 27,000, Polymorphonuclear count 80. Blood Chemistry: Chlorides 421, CO_2 72. Urine—occasional hyaline cast.

E. K. G. Reading: Auricular and Ventricular rate of 135 with normal rhythm; and very advanced degree of myocardial degeneration that is probably associated with coronary thrombosis. Simple tachycardia.

Upon reviewing the X-ray, laboratory and clinical findings, I ventured a diagnosis of volvulus of the stomach. My reasons for this diagnosis were: (1) Patient had an inverted stomach within the thorax for many years as seen on X-ray taken in 1927. The fluid level in the stomach persisted despite drainage via the Levine tube—nor did the gastric contents empty via the pylorus—suggesting an obstruction at both the pyloric and cardiac ends—Volvulus would produce just such a condition. (3) No abdominal distention—which meant no obstruction of the thoracic portion of the colon. (4) Absent bile in the gastric drainage indicating that the obstruction was not below the duodenum, else bile would have been backed up into the stomach.

Upon return from the X-ray room a Connell continuous suction apparatus was connected, with the hope that if the obstruction was not complete, the stomach could be emptied by continuous suction. More intravenous fluids were given. Oxygen tent to relieve dyspnea and cyanosis. Patient was urged to shift positions—to aid gastric drainage.

The question of surgery was approached but rejected by the family because he had always recovered from the previous attacks. Because of the serious condition of the patient a palliative thoracic procedure to empty the stomach with a trocar followed by suture and reduction of the volvulus was considered, with a more radical repair of the hernia proper at a later date. That evening his pulse rose to 125 growing weaker. Temperature 103, respiration 30. Stimulation was given. During the night condition grew progressively worse, and the patient died the following A. M.—38 hours after admission. Permission for autopsy was obtained and findings are noted below.

AUTOPSY REPORT

Very well developed, muscular, robust male, said to be 40 years of age and having the appearance of stated age.

Abdomen. On opening the abdomen there was found an old hernial orifice through the crura of the diaphragm. The sternum was removed in order to expose this hernia. The stomach, transverse colon and greater omentum were found to be in the left thoracic cavity, displacing the left lung towards the spine and apex of the chest. The right lung was compressed and the heart shoved over to the right chest, so that the left border of the heart was to the right of the right border of the sternum. The stomach was twisted on itself and pulled up into the chest so that the greatest constriction was just at the pylorus and the pylorus was on a level more cephalic than the cardia. The stomach was also twisted on itself so that the greater curvature, in the main, follows the left border of the sternum and the posterior wall of the stomach was plastered to the left chest wall. The greater omentum occupied the anterior portion o fthe chest and was adherent to the sternum and ribs. A large portion of the transverse colon was in the left chest and it lay posterior to the stomach. Apparently the hernial orifice was anterior to the esophageal opening in the diaphragm and separated by a fibrous septum from the cardia.

Stomach ligated and removed. It contains in excess of four quarts of fluid—this fluid was slightly blood stained. The rotation of the stomach was such as to cause tortion at the cardia acting as a stricture. The pylorus was incarcerated through the hernial orifice and the adhesions were rather dense at the orifice in the diaphragm. On removing the stomach, it was found to be greatly distended and there were mucous erosions, possibly due to stretching of the mucosa. There were no ulcerations or necrotic areas in either the stomach or transverse colon.

Thorax. Left lung shows complete atelectasis. Right lung was compressed, but shows no pneumonic areas.

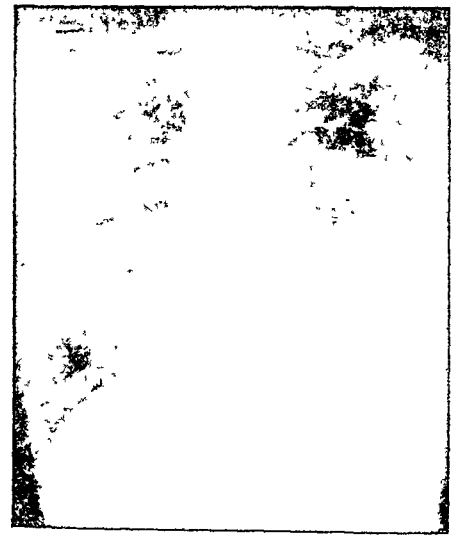


Fig. 4. Same as Fig. 3 after introduction of stomach tube and aspiration of fasting contents. Note: Diminution of gas bubble and expansion of lung.



Fig. 5. Stomach full. Oblique view. Duodenal bulb above cardia. Stomach completely inverted.

Heart normal in size. There were pericardial adhesions at various points.

Remaining abdominal viscera not remarkable.

PAST HISTORY

I am indebted to Dr. Zachary Sagal (7) for the following interesting details of this patient's past history. The patient was born in Crimea, Russia, and has always enjoyed good health. Upon careful questioning, however, it was brought out that while he had no difficulty in playing games with the boys, he could never keep up with them in climbing mountains or in any other strenuous physical exercises. In 1914 he was drafted into the Russian Army and was sent to the front. In January, 1915, while shooting in lying position on his abdomen on level ground, he was wounded in the lower back by a piece of shrapnel. He did not become unconscious, although he lost considerable blood. He was in a hospital for several months until the wound was healed. There was no paralysis or difficulty with rectal or vesical function. During his hospital stay he was X-rayed to determine whether any piece of shrapnel was remaining in his back, but none was found. He observed, however, that the doctors X-raying him showed great surprise and displayed unusual interest, demonstrating him to other staff members. He could not understand their conversations, but knows there was no fracture. After discharge from the hospital, he remained a war prisoner for three years and escaped back to Russia in 1918. Upon return to Russia he was confined to prison as a political suspect for a long period of time, and then managed to escape to Constantinople where he lived for over a year, and in 1922 he emigrated to America. In spite of all his hardships, he was always in perfect physical condition.

In September, 1925, after a heavy meal, he suddenly developed an attack of marked oppression in the chest and was only relieved after a hypodermic injection of a narcotic and after copious vomiting. A similar attack occurred in April, 1926. It was associated with nausea, severe pain in the back, profuse perspiration and headache. Physical examination revealed distant breath sounds in the left apex with few rales. There were elicited all the classical signs of hydropneumothorax of the left chest. He was again relieved by the administration of a narcotic and after vomiting. A medical consultant was called in and he also found signs of fluid and gas in the left chest and confirmed the diagnosis of hydropneumothorax. The question of etiology was not clear, whether it was due to pulmonary tuberculosis or was the result of the injury received in the war. He was referred to one of the largest hospitals in New York for observation and treatment. The following is the communication sent by the hospital in answer to Dr. Sagal's inquiry:

"Date of admission to hospital—April 29, 1926.

Date of discharge—May 11, 1926.

Diagnosis: Hydropneumothorax; pulmonary tuberculosis.

Last known condition improved.

X-ray report April 30, 1926: Examination of the chest shows a collection of fluid in the left chest extending up to the level of the fourth rib anteriorly. Above this there is a pneumothorax extending up to about the second rib anteriorly. Surmounting this the collapsed lung is seen, which shows no definite abnormality except perhaps some fibrosis. The heart and mediastinum are displaced to the right side.

Final note: Patient with a negative history who enters with complaint of sudden sharp pain in the chest one month before admission. On physical examination there is evidence of hydropneumothorax in the left chest which is confirmed on X-ray examination. Also some fibrosis seen at left apex. Sputum repeatedly negative. Repeated aspiration was unsuccessful."

He left the hospital against advice, refusing to submit to further paracentesis. The next attack occurred January 30, 1927, and was even more severe than the previous attacks. His pulse was weak and rapid—rate of 130. He was relieved by vomiting of large quantities of recently ingested food, and after an enema.

He was referred to Dr. Zachary Sagal on March 22, 1927. His findings were: "Physical examination was essentially negative except for the chest findings. He looked well-nourished, weighing 193 pounds, height 5' 11". Had good color but seemed to be somewhat short of breath. The apex of the heart was located one inch within the right nipple line and is diffuse. Percussion of the right side disclosed an area of relative dullness extending to the right nipple. The percussion of the left side showed



Fig. 6. Five hours after meal. Small residue in stomach. Splenic flexure of colon above and lateral to stomach. Cecum in right iliac fossa.

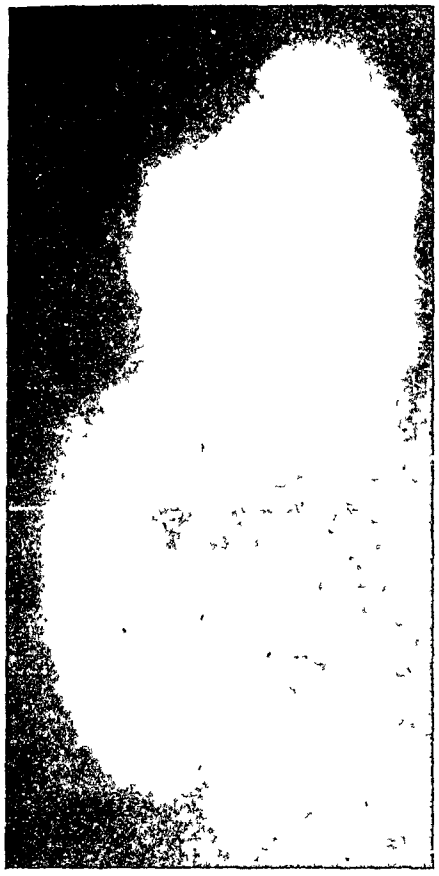


Fig. 7. Barium enema. Splenic flexure almost reaches the level of the left clavicle.

tympany in the upper half anteriorly as high as the clavicle. There is dullness over the left lower chest."

"X-ray examination of the chest shows a condition which very closely simulates hydropneumothorax (Fig. 2). However, there is no evidence of compression of the left lung. On respiration there is paradoxical movement of the upper level of the gas filled area. On close examination one can see some lung tissue through the gas. Re-examination after aspiration of the stomach reveals a marked change in the picture (Fig 4). The gas area is considerably lower, the fluid having disappeared and the lung in the left chest becomes more prominent. This occurs only when the stomach is emptied by means of a tube, but the fasting stomach (Fig. 3) shows a very large gas bubble. The left diaphragm cannot be seen, and the left base is quite dense."

"Upon administration of an opaque meal (Fig. 5), the stomach is seen to be filling in water-trap fashion, is completely inverted, the cardia being just above the level of the diaphragm, the lower pole occupying the highest portion in the chest. The pylorus and first portion of the duodenum lie mesial and behind the cardia, crossing it on entering the abdominal cavity. Further study reveals that part of the colon is also in the thoracic cavity. It required two large films to take a roentgram of a barium enema, as the colon extends from the right iliac fossa to the left clavicle (Fig. 7). There was no disturbance in the motility of the stomach or intestine. The left diaphragm could at no time be definitely visualized and is entirely absent or deficient to such an extent as not to be demonstrable."

The patient had no trouble until January, 1929, when another severe attack occurred. He was readily relieved after evacuation of the stomach. Another attack occurred in August, 1931, and also was relieved.

Comment: There is nothing in the history to suggest that the condition was due to trauma. The shrapnel wound was sustained when the patient lay flat on his abdomen, and he was hit from above. Rupture of the diaphragm usually occurs when a severe blow is dealt on the abdomen, or when the abdomen is severely compressed, neither of these conditions having occurred. Nor are there any symptoms indicating respiratory or circulatory embarrassment, as would be the case in sudden extensive herniation of the abdominal viscera into the thorax. He had no difficulty in his adult life, and withstood the rigors of army regime. Judging from the description supplied by the patient and the attending physicians, the attacks were probably due to recurring volvulus of the stomach which untwisted itself under the relaxing effect of narcotics or by change of position by the patient. One can readily visualize how the stomach in its inverted position when overloaded, may sag and by its own weight close off both the cardiac and pyloric orifices.

Dr. Sagal (7) reported this case in the American Journal of Roentgenology and Radium Therapy as a case of "absence of left diaphragm with inverted thoracic stomach." The reported case is not the only one in which the presence of the stomach in the thorax was mistaken for tuberculosis and hydropneumothorax. Truesdale (8) in 1921 operated on a child of five who was run over by an automobile nine months previously. The child had spells of dyspnea, cyanosis, and distress after eating. He was examined by many physicians who concluded the child had tuberculosis of the lungs with cavity formation. The left thoracic cavity was found to contain the stomach, small intestines, colon, left lobe of the liver and spleen.

O'Dwyer (9) in 1889 operated on a child of three who had a congenital diaphragmatic hernia. The case had been diagnosed as purulent pleurisy. Thoracotomy was done and a diaphragmatic hernia containing small intestines was found.

Giustinian and Antonelli (10) (1931) report a case of an infant twenty-two months old who was admitted with a diagnosis of bronchitis and pleural congestion with serofibrinous pleurisy. A double pleural puncture at the seventh and eighth intercostal spaces yielded a few drops of serous fluid. X-ray seven days after admission did not clear up the diagnosis. Autopsy revealed the greater part



Fig. 8. X-ray taken October 10, 1935, shows Levine tube in esophagus, stomach greatly dilated, occupying most of thoracic cavity. Marked displacement of heart.

of the right hemithorax occupied by the small intestines, cecum, appendix, ascending colon and middle part of the transverse colon.

Struppler's (11) case had nineteen exploratory punctures before the correct diagnosis was made. Truesdale (8) cites a case in which milk was aspirated from the chest by exploratory puncture. Lebon (12) reports two cases of false pneumothorax, one in a soldier who had the stomach punctured twice by parancentesis thoracis. Likewise, Stivelman (13), doubting the diagnosis of pneumothorax in a tuberculous patient, administered a barium meal and found the case to be one of eventration.

The opaque meal and roentgenoscopy should never be omitted after a careful analysis of the history and physical findings make one doubtful of the presence of a *hydropneumothorax.*

Ball (14) (1935) has suggested having the patient swallow "Seidlitz Powder" to generate gas in the stomach for contrast in fluoroscopic and X-ray examination.

SUMMARY

A case of diaphragmatic hernia has been presented with a history of chronic recurrent attacks of partial obstruction of an inverted intra-thoracic stomach in whom clinical and X-ray findings led to a mistaken diagnosis and treatment for tuberculosis and hydropneumothorax with repeated paracentesis, and the final development of acute complications due to volvulus of the stomach with acute dilation sufficient so to embarrass the heart and lungs as to cause death, with autopsy findings to substantiate clinical and X-ray findings.

CONCLUSIONS

1. The symptoms and physical signs of diaphragmatic hernia are varied and complex; clinical diagnosis is difficult without X-ray examination.
2. Diaphragmatic hernia is frequently mistaken for disease of the gall bladder, stomach, heart and lungs.
3. Obscure chest and abdominal symptoms demand X-ray of the gastro-intestinal tract as well as of the chest to rule out hernia.
4. Respiratory difficulty and recurrent obstructive symptoms in infants and children should lead to a suspicion of diaphragmatic hernia.
5. Diaphragmatic hernia should be suspected in crushing injuries of the chest and abdomen.
6. The mortality of those operated on before obstruction has occurred has in recent years not been higher than that of other abdominal operations.

The author wishes to express his indebtedness to Dr. Zachary Sagal for the details of the patient's past history and for his kindness in forwarding me negatives of the films used as illustrations in this article.

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SECTION V—*Therapeutics*

Chaulmoogra Oil in the Treatment of Lymphopathia Venerea*

By

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LYMPHOPATHIA venerea continues to be the greatest etiological factor in the cases of *rectal stricture* seen in this clinic. Dr. Collier F. Martin (1) in 1935 ably explained the reason for the greater incidence in the female negro in this clinic.

Lymphopathia venerea is a virus infection transmitted in most instances through venereal exposure. The site of the initial lesion in the female is commonly either the fourchette, the posterior wall of the vagina, or the posterior lip of the cervix. From these foci the infection spreads posteriorly to the perirectal lymph nodes and lymphatic network. The process goes on from lymphangitis with round cell infiltration to the formation of miliary abscesses in the rectal wall. The tissues react with the loss of some of the mucous membrane as some of the small abscesses perforate into the lumen of the rectum. Fibrosis develops around these miliary abscesses and sinuses. The result is either a band-like or tubular stricture of the rectum. The large majority of patients give a positive reaction to the Frei test.

Most of these unfortunate patients are not seen until the process is well advanced, presenting symptoms of constipation, blood and pus in the rectal discharge. Eventually most of these patients with stricture require colostomy.

Stannus (2) states: "In no known virus disease is there any specific chemo-therapeutic treatment at present available and lymphogranuloma inguinale appears to be no exception to this general rule." Never-

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theless, when one sees a disease which eventually kills the patient, it is quite natural to try experimental therapy with agents which have been of value in other diseases with similar pathology. With this consideration in mind, Doctors Collier F. Martin, Robert Hunter and Harry Z. Hibshman suggested the therapeutic use of chaulmoogra oil in patients with lymphopathia venerea. They recognized a parallelism in some of the pathological characteristics of this disease and leprosy such as granulomatous changes, hypertrophies of the skin, abscesses and fistulae. A study of the clinical changes, if any, following the use of chaulmoogra oil in the course of treatment of these patients seemed desirable.

A series of patients was selected for this study. Each gave positive Frei reactions and suffered from some type of anorectal pathology. The patients were given intramuscular injections of chaulmoogra oil, from one to two cubic centimeters per dose, once or twice a week for from four to six weeks. Clinical changes in the appearance of the local lesions and in the general well being of the patients were noted during the course of treatments and six weeks after discontinuance of the treatment.

Case 1. L. J. The patient a negro female of twenty years, single, was first seen in the clinic in October, 1935, complaining of constipation, pain during and after bowel movements, and occasional appearances of blood at time of stool. She had a posterior anal ulcer, moderate congestion of the rectal mucous membrane, and beginning thickening of the posterior wall of the rectum above the anorectal line. She gave a positive Frei reaction and negative reactions to the Wassermann, Kolmer and Eagle tests. The anal ulcer and infected crypt above the ulcer were excised. Although the patient complained of less pain following operation, the wound healed very slowly. Excessive granulation tissue recurred over a period of three months in spite of its removal by cutting and the application of strong solutions of silver nitrate. From January 25, 1936, to March 14, 1936, she was given eight intramuscular injections of chaulmoogra oil. Her general condition at the time of the last injection seemed better. She stated that she felt stronger and had more energy. The cutaneous portion of the operative wound had healed from without inward to a point midway between the anal margin and the anorectal line. Proctoscopic examination revealed an ulcer posteriorly with indurated margins in the upper part of the anal canal. For a distance of four to five centimeters above the anorectal line was seen a moderately severe ulcerative proctitis with patches of fibrinous exudate. There was no improvement noted when seen six weeks later. The patient was aware of a rectal discharge of blood, pus and mucus. The proctoscopic examination gave the same picture of ulcerative proctitis with beginning fibrosis in the posterior wall, a forerunner of rectal stricture.

Case 2. R. D. The patient, a negro female, twenty-nine years, single, was first seen in November, 1934, complaining of difficulty with her stools and of the escape of gas from an opening in the perineum between the anus and the vagina. She had an anterior anorectal fistula, a posterior anal ulcer, and an annular rectal stricture about six centimeters above the anal margin. The Frei reaction was positive and the Wassermann test negative. The ulcer and fistula were excised in September, 1935. The posterior wound healed in about six weeks, but the anterior wound did not heal. There was a return of the discharge in the anterior wound and the appearance of excessive granulation tissue was noted. On January 25, 1936, the rectum admitted a number 18 Hegar dilator with discomfort to the patient. She was given weekly doses of chaulmoogra oil, one cubic centimeter intramuscularly, for seven weeks. During the third week she complained of an attack of diarrhea. Since none of the other patients in this series complained of diarrhea, little significance was paid to this symptom. About the fourth week the skin wound had nearly closed and there was very little purulent discharge from the wound. However, during the sixth week the wound began to discharge more freely with breaking down of tissue. There was of course no improvement as far as the stricture itself was concerned. There was a moderate amount of ulceration of the mucous membrane in the region of the stricture. She was examined again six weeks later with no evidence of further improvement.

Case 3. R. M. The patient, a negro female, forty-nine years, widow, was first seen in this clinic in November, 1929, complaining of difficult bowel movements. She first noticed constipation when she was a resident of Texas at the age of twenty-one years. In 1910 she had a hemorrhoidectomy. In 1911 she had an anterior anorectal abscess, which was promptly excised. After removal of sutures, she noticed drainage from the vagina as well as from the rectum. At that time a diagnosis of rectal stricture was made, and the condition was treated by dilatation with sounds. Her condition has become progressively worse. Upon admission to this clinic, she was found to have an advanced tubular stricture of the rectum of extremely narrow calibre with discharge of blood and pus from the vagina and rectum. She was required to take saline laxatives to keep the stools liquid. She also had a rectovaginal fistula. She was advised to have a colostomy, and after some delay, her consent was obtained and the operation was performed in September, 1930. Her general health improved, but the fistula persisted. The fistula was excised later in 1930. A pathologist reported the excised tissue as being tuberculous. In 1931 she developed extensive hypertrophy of the vulvae. The left labium majorum was removed in October, 1931. She was more comfortable for a few months, but later ulceration of the cutaneous surfaces and of the mucous membranes involving both labia minora, clitoris, and rectum developed. A Frei test was done May 10, 1933, which gave a definitely positive reaction. A diagnosis was then made of lymphopathia venerea with rectal stricture, rectovaginal fistula, esthiomene, and cutaneous ulceration. Six operations were done in 1931 to remove painful ulcerative lesions. In November, 1935, she was in considerable pain, had become gradually weaker, and was very much depressed and discouraged. In December, 1935, the right labium majorum was removed, from which an antigen was prepared. She was given five or six intravenous injections of 1:1500 solution of hydrochloric acid during the latter part of December, 1935, and the early part of January. There was a marked improvement in her general condition and less discharge from the wound which had a healthier appearance. On January 25, 1936, injections of the hydrochloric acid were discontinued and chaulmoogra oil, one cubic centimeter intramuscularly, were given once a week. February seventh she complained of more pain in the wound and more purulent discharge. She was depressed and had lost weight. On April fourteenth the injections of hydrochloric acid solution were resumed. Six weeks later she stated that she felt better. There was no material improvement at that time in the condition of the ulcerative lesions. There was slightly less purulent discharge.

Case 4. H. L. The patient, a white male, fifty-five years, single, a trolley conductor, was first seen in our clinic in November, 1935, complaining of itching and moisture around the anus for the past six or seven years. He had been operated upon fifteen years ago for rectal fistula in a Philadelphia hospital. He stated that he was well for several years after the operation, although the wound healed slowly.

Examination revealed a short anorectal sinus. No external fistulous opening was demonstrated at the time of

examination. He had, however, a posterior anal ulcer and inflammation of the over-lying crypt which were removed by endotherm December 30, 1935. Although he gave no definite history of a venereal bubo, he had had five different herniorrhaphies. On January 2, 1936, Frei tests were done with positive reaction. The wound healed slowly. There was no evidence of rectal stricture. Beginning January 23, 1936, he was given weekly injections of chaulmoogra oil intramuscularly. February twenty-ninth it had apparently healed. April fourteenth he was re-examined and it was found that the wound had broken down with a discharge of pus.

Case 5. A. T. The patient, a negro female, married, thirty-one years, factory worker, had been admitted at this clinic in 1934. At that time she had a tubular stricture and gave a positive Frei reaction (July 8, 1934). Her husband was tested about three weeks later and likewise gave a positive reaction to the Frei test. The stricture had been treated by the carbon dioxide method with favorable results for several months as far as the calibre of the stricture was concerned. In 1932 she had an anorectal abscess.

She returned to this clinic in January of this year complaining of extreme weakness, palpitation, tachycardia, was anemic, and was given an iron tonic. The rectal examination revealed a tubular stricture of the rectum beginning six centimeters from the anal margin. There was elephantiasis of the right labium minorum. February tenth treatment with chaulmoogra oil was begun. She received weekly injections for a period of five weeks. There was an increase in the hemoglobin content. There was no improvement as far as the ulceration in the mucous membrane of the rectum was concerned. The stricture was relieved by dilatation with sounds.

Case 6. L. V. The patient, a young negro woman, twenty-three years, was first seen in January, 1936. She was a native of Savannah, Georgia. At the age of thirteen she began to have illicit sexual relations and became pregnant, giving birth to a child when fourteen and one-half years old. She married in 1931 and has had no further pregnancies nor miscarriages. She stated that she had "piles," about that time, but received no treatment. In 1933 she began to complain of constipation which became increasingly marked. She had ribbon stools, and required the use of saline laxatives to permit defecation. She noticed a discharge of blood and pus accompanying her stools. During the past year she has noticed a purulent discharge from the "external piles."

On inquiry her husband admits having had a sore, the size of a large pea, on the dorsum of the shaft of the penis. He was given a Wassermann test, which was 4 plus. He had enlarged lymph nodes in the left groin. He had phimosis and was circumsized and received a course of twelve injections of arsphenamine. Examination, when seen on March 20, 1936, revealed no evidence of buboes, except some palpable inguinal nodes. He was given a Frei test with several strains of antigen. He gave a positive reaction. His Wassermann reaction was still positive and he was advised to continue his antiluetic treatment.

The wife (L. V.) was found to have an advanced rectal stricture with three hypertrophied and fistulous anal skin tags, which the patient mistook for "piles." She was given a Frei test with several strains of antigen and gave a strong reaction. She was given six intramuscular injections of chaulmoogra oil weekly and although there seemed to be less secretion for about two weeks, there was no improvement in the rectal pathology of stricture with proctitis and ulceration. The rectum will admit a number thirteen sound with some difficulty.

COMMENTS

Our problem was to determine whether or not any therapeutic benefit might follow the use of chaulmoogra oil in lymphopathia venerea which pathologically resembles leprosy. Chaulmoogra oil is a mixture of chaulmoogric, hydnocarpic, and palmitic acids. Sollman (3) attributes the beneficial action of chaulmoogra oil in the treatment of leprosy to the selective toxic effect on the acid-fast bacilli (B. Leprae). It is therefore superfluous to expect any such selective action of these acids on the virus of lymphopathia venerea.

The patients with lymphopathia venerea have shown no consistent improvement following injections of chaulmoogra oil. Some of the patients showed a response with an attempt to heal skin wounds following fistulectomy, but the result was not permanent. In many cases there was an increase in the amount of purulent discharge from the fistulous tracts. Patients with rectal stricture showed no improvement. There was no improvement in the condition of the mucous membranes involved. Our experience, therefore, with chaulmoogra oil is that it is of no value in the treatment of lymphopathia venerea.

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SECTION VII—*Surgery of the Lower Colon and Rectum*

Lymphogranuloma Inguinale: Rectal Stricture and Pre-Stricture*

By
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THIS *paper constitutes a three year clinical study* of 115 cases of Frei positive lymphogranuloma inguinale strictures in a total consecutive series of 138 rectal strictures observed by us in the Cook County Hospital Gastro-Intestinal-Rectal Clinic.

ETIOLOGY

Predisposing Causes. Age. Of the 115 Frei positive cases studied, the youngest patient was 22, the oldest 57. The most common age was from 25 to 35. There was no significant difference in age distribution between male and female sexes. The views of other observers that lymphogranuloma inguinale is contracted in the age of most sexual activity is also noted by us in this stricture series.

Race. One hundred and four (or 90%) of our patients were Negroes, 10 (10%) white, and 1 (1%) Mexican. Ninety-eight (95%) of the females were Negroes; 5 (5%) were white. Only 5 (42%) of the males were Negroes; 6 (50%) were white; 1 (8%) was Mexican.

There is a general agreement in this country that the rectal stricture phase of this malady is most common in the colored race, especially in the colored female. Rosser (1) advanced the theory that the prevalence of stricture in the Negro may be accounted for partly by the racial predisposition to develop massive inflammatory deposits, which tendency he named "fibroplastic diathesis." Rosser also believes that the Negro is particularly susceptible to venereal infection as the result of the social conditions under which he lives.

Sex. One hundred and three (or 89%) of our patients were females, 12 (11%) males. A somewhat similar sexual incidence of rectal stricture has been remarked by nearly all observers.

Venereal factor. None of our female patients were virgins, in fact most were quite loose sexually.

Exciting cause. Of the total of 138 rectal strictures studied, 115 were found to have a Frei positive test (2), and form the basis for this report. Of the remaining twenty-three strictures, six were found by biopsy to be rectal carcinomas, four were due to nonspecific ulcerative colitis, two were post-operative anal stenoses, and eleven were of undetermined etiology. Of the 115 Frei positive stricture cases, seventeen (15%) also had a positive Wassermann. Twenty-six (22%) had a positive complement fixation test for gonorrhoea. Eight (7%) had a positive Frei, a positive Wassermann and a positive gonorrhoeal complement fixation test. There was no evidence of tuberculosis clinically or on X-ray of any of our patients. Biopsies made from the stricture in patients selected at random from our group, in no case showed any evidence of either syphilis or tuberculosis. We did not test our patients for chancroidal infection with Dmelcos vaccine because of the difficulty in obtaining the vaccine in this country.

CLINICAL COURSE OF LYMPHOGRANULOMA INGUINALE

We wish to emphasize that this is a venereal disease caused by an ultramicroscopic filtrable virus, with a primary lesion appearing on the external genitalia and secondary spread by way of the lymph channels to the lymph glands draining the region. In the male, lymph drainage is, on the whole, to the inguinal glands, so that bubos are common. In the female, lymph drainage is preponderantly to the glands of Gerota surrounding the rectum, producing a periproctitis and an obliterating proctitis or stricture. Because the lymphatic channels are liable to a good deal of variation as to their distribution and because the location of the initial lesion is variable, several types of lymphogranuloma inguinale lesions may develop in the female. We have noted (A) a "pre-stricture" lymphogranulomatous proctitis; or (B) a stricture with or without other complications. Associated with definite rectal stricture there may be (C) "cock's-comb" anal skin tags; (D) perianal "watering pot" granuloma with sinuses and fistulae; or (E) elephantiasis of the vulva (esthiomene or genito-ano-rectal syndrome); (F) a chronic lymphogranulomatous parametritis or pelvic cellulitis may be present with or without a rectal stricture; (G) stenosis of not only the rectum but the entire colon. Finally any and all combinations of the above types may be noted in any one patient. Table I shows these listed in the order of frequency of their occurrence in our series.

In our entire series, none could recall the initial lesion. The incubation period could not be determ-

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Submitted October 12, 1936.

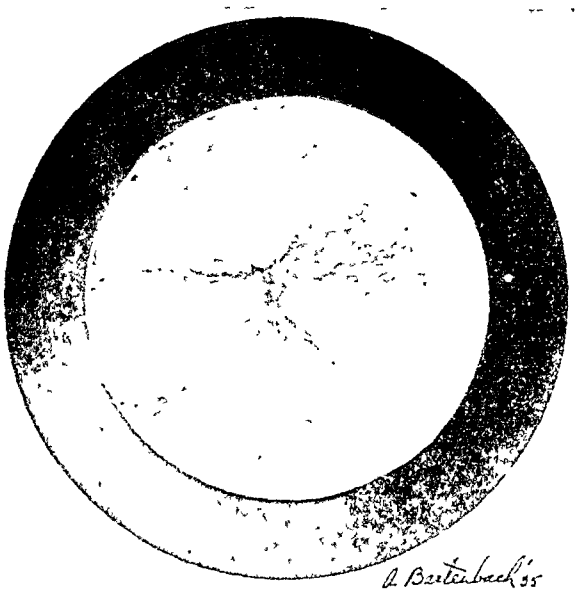


Fig. 1. Proctoscopic view of anal canal leading to a Frei-positive stricture. Note the cone-shaped narrowing leading to the stricture opening; the superficial ulceration and the hypertrophied papillae at the base of the cone (pectinate line).

ined. Only 30 patients (26%) could recall an inguinal bubo. The duration of rectal complaints varied from 4 weeks to 19 years. It is our present impression that rectal strictures are slow to develop and may take years to reach the stage where they produce symptoms.

Pre-stricture. Since we were on the lookout for cases of lymphogranuloma inguinale with early rectal involvement, we had the good fortune to recognize 7 Frei positive early proctitis cases where stricture had not as yet developed. We have designated this type as the "pre-stricture" stage of rectal lymphogranuloma inguinale. (Since the completion of this paper, we have seen 7 additional cases of the "pre-stricture" stage). Some of these patients were symptom free, and the lesion was discovered accidentally. Others complained of bloody or purulent rectal discharge, pain on defecation or of constipation. In these patients, digital examination elicited a somewhat thickened, infiltrated, inelastic rectal wall which contained scattered granulomatous nodules of varying size, starting about 5 cm. above the anal verge and extending upward for a varying number of centimeters. Proctoscopic examination showed erosions and the above purple-red granulomatous nodules which bled easily on instrumentation. Biopsies made from the rectal wall showed a picture of chronic inflammation identical with that seen in the stricture stage (biopsy findings will be discussed in more detail later).

Stricture. As a result of continued inflammatory processes and contraction of cicatricial tissue, the bowel lumen slowly diminishes, and a stricture forms. When the stricture stage is reached, patients complained of progressive increasing constipation, difficult and occasionally painful defecation, straining at stool, often of pencil or ribbon feces, bloody and pussy discharge (often present even when not at stool), abdominal cramps and bloating, sometimes loss of weight, and sometimes of perianal or vulvar swellings. Although constipation was the rule, some patients complained of intermittent diarrhea and constipation. In many cases, patients were obliged to take increasing doses of saline cathartics in order to void a liquid stool, the only form they were capable of passing through their diminished rectal lumen. Nine patients of our series underwent colostomy, 2 of their own free will and 7 because of obstruction. It is interesting to note that none of our female patients became pregnant during the known period of their stricture. Also, only two patients had any previous pelvic surgery.

On inspection of a simple uncomplicated lymphogranuloma inguinale stricture the peri-anal area appears perfectly normal with the fatty cushions practically intact.

Digital examination frequently elicited a patulous anal opening and a cone-like narrowing which tapered down to the stricture entrance 3 to 8 cm. above the anal verge. The anal cones often felt smooth, hard, and cicatricial ridges; others hypertrophied papillae, and cicatricial ridges; others hypertrophied papillae; while others presented combinations of any or all of the aforementioned findings.

In 76 patients (66%), the distal end of the stricture was located from 4 to 6 cm. from the anal opening. In 28 patients (24%) it was from 2.5 to 4 cm., and in 10 patients (9%) from 6 to 8 cm. from the anal verge.

When the opening was penetrated by the examining finger, a tubular stricture with irregular constrictions and pockets was felt. The walls were somewhat irregular and fibrous. In some cases polypoid or granular nodules were palpable. Pressure on some portions of the wall often caused the finger to break into lateral sinuses or small cavities which had been incompletely obliterated by friable adhesions which gave way to the examining finger. In most cases we were not able to reach the upper portion of the stricture. In an occasional patient, the finger passed through the upper extremity into a dilated portion of the upper rectum.

Proctoscopic examination revealed a gradually increasing cone-like deformity of the anus and rectum which led up to the stricture opening. The anal mucosa

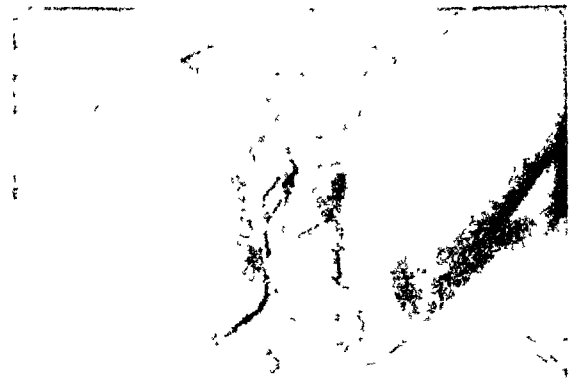


Fig. 2. M. C.: Mexican female. Rectal stricture complicated by elephantiasis of the left vulva; elephantiasis of the peri-anal area; and peri-anal granuloma with "watering-pot" sinuses.

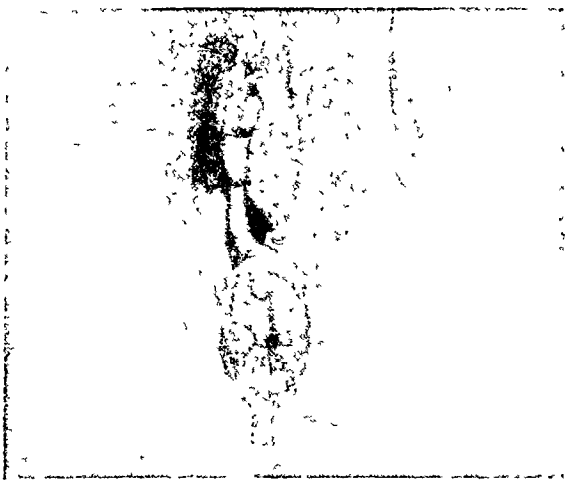


Fig. 3. H. M.: Colored female. Rectal stricture complicated by "cock's comb" anal bouquet and elephantiasis of the vulva.

was usually somewhat reddened, and presented small, ill-defined, pink-red, scattered, irregular areas of superficial ulceration. There were often blueish-white, firm scars.

A few small nodules or papilla-like strictures were often visible on the surface of the mucous membrane leading to the stricture opening as well as on the walls of the stricture proper. Frequently, congested blueish-red hemorrhoids were noted just inside the anal opening. Cryptitis, papillitis, and fissures were sometimes present.

The mouth (and as much of the walls as were visible) of the stricture presented reddened, granular mucosa, bleeding on the slightest pressure, often with firm blue-white, transverse cicatrices. Scattered areas of ulceration were present similar to those described in the anal canal. Occasionally a polyp could be seen (Fig. 1).

A blood tinged muco-purulent "cherry-juice" discharge commonly exuded from the stricture lumen. This apparently arose from lateral sinuses and abscesses which were ulcerated and infected; some of it may have come from stercoral ulceration above the stricture.

Associated lesions. In our series, sinuses and fistulae were the most frequent associated lesions found, being present in 31 patients, or 27%. In extensively complicated cases, large, thick, india-rubber-like granulomas perforated by draining sinuses were noted beside the anal opening. (Fig. 2) "Watering-pot" fistula, "cock's comb" skin tags (Fig. 3) were frequently present and occasionally vulvar elephantiasis was seen (Fig. 4).

With all this pathology, there was an anal lack of pain or tenderness of the involved parts. Also, there was rarely much impairment of the general health in spite of the apparent intractable chronicity for as long as fifteen years.

Laboratory findings. Results of Frei, Wassermann, and gonorrhea complement fixation tests have already been discussed. In 25 patients taken at random from our series, red blood counts ranged from 2,800,000 to 4,200,000. The associated hemoglobin ranged from 30% to 70%, giving in every instance the picture of a secondary anemia. White blood counts ranged from 6200 to 9350. The monocyte count ranged from 4% to 9%. X-ray studies of the chest were uniformly negative for tuberculosis. Twenty-five of our patients selected at random were given the usual type of barium enema and roentgenograms made to determine length, caliber, lateral ramifications and general appearance of lymphogranuloma inguinale strictures. The length varied from 3 to 14 cm. with an average of about 7.4 cm. Although the cone formed by the anal canal and lower rectum at the distal end of the stricture was not visualized by the films (probably due to the patulous anal sphincters so often present in these cases) a similar cone was often present at the proximal end of the stricture. (Fig. 5). In some cases an actual pouch was present above the stricture. A very important roentgen finding was the frequency of lateral sinuses leading from the stricture. (Figs. 5 and 6). In some cases actual abscess cavities were noted at the end of these sinuses. (Fig. 6). It is our impression from the clinical findings of a large number of such patients that many of these lateral sinuses do not communicate with peri-anal fistulous openings and drain into the stricture lumen proper.

Biopsies were made upon tissue from 50 of our patients selected at random. Microscopic changes were those of a non-specific inflammatory reaction. The tissues usually showed a diffuse infiltration by lymphocytes, epithelioid cells, plasma cells and polymorphonuclear leucocytes, as well as an occasional foreign body giant cell. (Fig. 7). In some, inflammatory changes were marked, whereas in others they were of a milder nature. Cellular infiltration was often peri-vascular. Many new capillaries were present. Dilated lymph channels were occasionally seen. Some connective

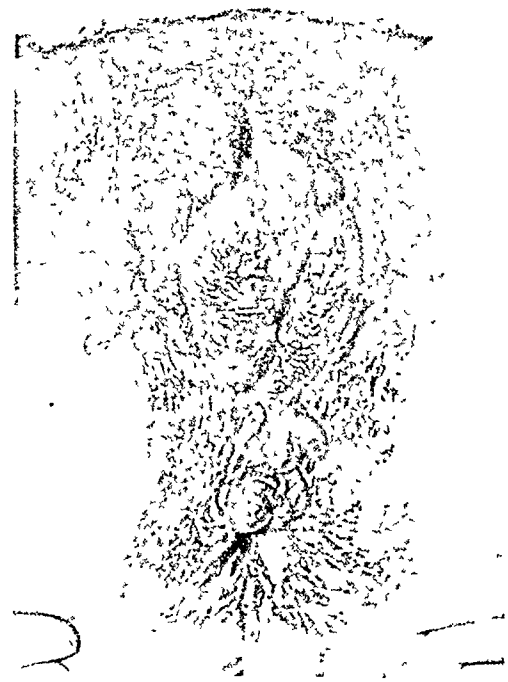


Fig. 4. Rectal stricture complicated by elephantiasis of the vulva and anal skin tags.

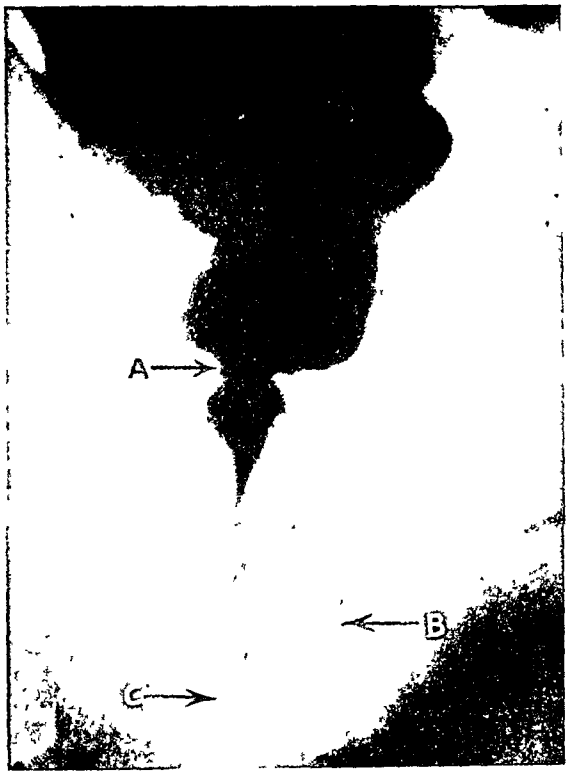


Fig. 5. X-ray of Frei-positive rectal stricture showing peri-rectal sinus (B); proximal cone of stricture (A), and location of anal opening (C).

tissue proliferation was usually found in those cases of longer duration.

TREATMENT

Although we realize that no existing specific treatment is available for lymphogranuloma inguinale stricture patients, yet a number of medical and surgical procedures can be carried out to improve the local and general condition of these individuals.

The following treatment has been reported by other investigators with varying degrees of results. Weekly intravenous injections of 10 c.c. of a 1% antimony potassium tartrate; fuadin intravenously once weekly starting with 3.5 c.c. at the first injection, followed by 5 c.c. every other day for a total of 12 injections. Stibenyl in 5 to 20 c.c. doses intravenously on every other day. Lugol's solution has produced some improvement in a few cases. Cuprosol in doses 1.5, 2.5 and 3.0 c.c. given alternately with Stibenyl. Solganol 0.01 to 1.0 in water solution intravenously every second day. Introcoid which has been used in Hodgkin's disease is administered in 2 to 10 c.c. doses intravenously at 2 to 5 day intervals, using a total of 60 c.c. Sodium salicylate 6 to 8 grams daily given orally, keeping the patient on a milk diet or ½ to 1 gram in glucose solution is given intravenously daily for as long as 30 days, with a normal diet.

Saline laxatives, castor oil, mineral oil, various tonics, vaccine therapy, serum therapy, bouillion filtrates, hydrotherapy, finger dilatation, short wave radiothermy, X-ray and radium have been used.

Our treatment has consisted of the following medical and surgical procedures. While we have encouraged a low residue, high caloric, high vitamin diet, the economic status of all of our patients prevented them from eating anything but the usual emergency relief food. Mineral oil ½ ounce, b.i.d., was given to facilitate easier, more complete and less painful defecation.

Twenty-five of our patients, selected at random, were given from ten to twenty-five intradermal antigenic vaccine treatments by Wien and Perlstein of the Cook County Hospital Skin Department over a period of a year to a year and a half. Because these patients received finger dilatations, daily enemas, and other treatment, it was difficult to evaluate the exact effect of the vaccine therapy.

However, it was our impression that the vaccine therapy did produce some clinical improvement. Biopsies made before treatment was started and repeated after the vaccine therapy had ended showed only a change toward a more chronic type of granulation tissue. Cellular infiltration changed from a mixture of polymorphs and round cells to an infiltration by lymphocytes and plasma cells; the number of capillaries present had decreased. The essential type of lesion, however, remained unchanged.

Daily hot sitz baths seemed to be of some value. All our patients were instructed to use daily cleansing enemas of a quart of either 1/7500 potassium permanganate or 1/5000 mercurochrome solution. Such enamas served to clean out pus and infectious ma-

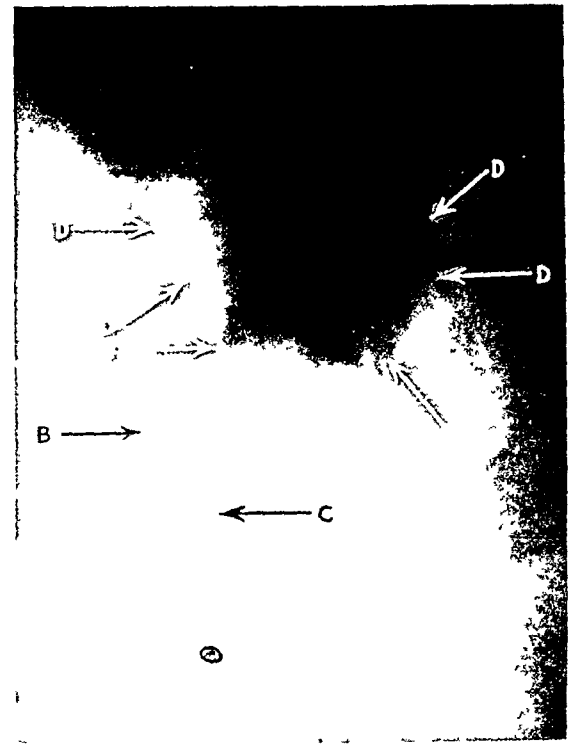


Fig. 6. X-ray of Frei-positive stricture showing peri-rectal sinus leading to an abscess cavity (B); dilatation of bowel (DDDD) above stricture; proximal extremity (A) and distal extremity (C) of stricture.



Fig. 7. Biopsy from an Elephantiasis of the Vulva—(High Power). Lymph channel; prominent endothelium; round cells about lymphatic channel consisting of A—fibroblasts, B—plasma cells, C—lymphocytes.

terial, deodorized and perhaps encouraged healing of the inflamed mucosa.

Careful finger dilatation was the only form of routine stricture stretching that we practised, and was performed once weekly or every two weeks. Graduated Wales bougies have not been used by us in these cases because occasionally such treatment results in perforation of the ulcerated gut above the peritoneal reflection, with resulting peritonitis and death. Although there has been considerable controversy as to the advisability of surgical intervention in lymphogranuloma inguinale, our experience in selected cases has been highly satisfactory.

Wien and Perlstein (3) have noted that patients with lymphogranuloma inguinale are very poor surgical risks unless first treated with Frei antigen. We have followed their suggestion and have operated only upon those who have previously received such a course of treatment.

Edematous skin tags, anal fissures, sinuses, fistulae, (anal, ano-rectal; recto-vaginal) perianal granulomas and elephantiasis of the vulva have been successfully operated upon, in about 18 of our cases. Two of our cases required posterior proctotomy to prevent complete stenosis. Operations for fistula which involve the sphincter should be done in graded stages to prevent incontinance.

Some cases heal rapidly, while others take many weeks. The constant bathing of the wound by the "cherry-juice" rectal discharge seems to prolong healing in most cases. In one case a large watering-pot granuloma was excised and healed by first intention. In this same case an elephantitio vulva was excised, and a recto-vaginal fistula repaired with good results in spite of the existing active pyogenic discharge.

We have never urged colostomy in these cases because most of the patients are young females; however, two became thoroughly discouraged with weekly dilatations and requested colostomy. Eight other patients became completely obstructed and required a colostomy making a total of ten in all who were colostomized. Two cases in our series have had posterior resections following colostomy, one done by Marshall Davison and the other by R. W. McNealy. Fig. 8 shows one of these specimens.

J. L. Jelke (4) in 1931, presented a unique drainage treatment for rectal stricture which promises to be of considerable value in lymphogranuloma inguinale stricture cases. H. C. Bacon (5) in 1934, discussed

TABLE I

Rectal stricture with complications—115 cases (103 females, 12 males)

A—Prestricture stage	
7 females of the 103	
1 male of the 12	
B—Rectal stricture (uncomplicated)	
44 females of the 103	
2 males of the 12	
C—Rectal stricture with anal growths or anal tags (cock's comb)	
19 females of the 103	
4 males of the 12	
D—Rectal stricture with sinuses, fistulae or granulomas (watering pot)	
30 females of the 103	
5 males of the 12	
E—Rectal stricture with elephantiasis, anal growths, sinuses (esthiomene)	
6 females of the 103	
0 males	
F—Rectal stricture with pelvic pathology	
17 females of the 103	
G—Stricture of the entire colon	
1 female of the 103	
0 males	
H—Rectal stricture with associated complications	
Pellagra—1 case	
Pemphigus—1	
Bacterial endocarditis—1	
Acute nephritis—1	
Chronic nephritis—1	
Carcinoma of the pylorus—1	
Rheumatoid arthritis—2	



Fig. 8. B. N.: Frei-positive stricture in a young colored female removed by posterior resection. Note the anal verge skin and hairs; the narrow scarred stricture proper and the dilated ulcerated bowel above.

the rationale of this operation and reported symptomatic improvement in all cases.

CASE REPORT

(This is an unusual case in which autopsy showed lymphogranuloma inguinale involving the termial ileum and colon as well as the rectum).

D. M., colored female, age 40, complained of constipation and of a purulent and bloody rectal discharge all of 13 years duration. Stools had gradually become narrow and flattened. For the past six months weakness, anorhexia, nausea, loss of weight, lower abdominal cramps, and occasional lower left quadrant abdominal pain had been present. Bilateral "pus-tubes" had been removed four years ago, according to the patient.

The patient was undernourished, moderately ill and showed evidences of marked weight-loss. Proctoscopic examination revealed a pipe-like and fixed rectal wall with a nodular constriction at 4.5 cm. which barely allowed the passage of the proctoscope. The mucosa was scarred, granular and nodular, with irregularly scattered, chronic ulcerations. Frei test was positive, Wassermann negative, G.C. complement fixation test negative, stool culture negative, RBC 2,900,000, hemoglobin 45%.

She developed marked tenderness over the lower abdomen, then one day suddenly complained of diffuse abdominal pain, became comatose, her temperature rose to 101° F. and she died twelve hours later.

Autopsy revealed the small intestines to be lined by light yellowish tan mucosa. In the terminal portion of the ileum there were three transverse defects in the mucosa, measuring up to 3 cm. in diameter. The edges of these defects were smooth and the floor was light yellow and smooth. The mucosa of the large intestine was pale pinkish gray and in the descending colon presented irregular whitish scars.

The rectal mucosa was light purplish gray in color and irregularly scarred. Scattered throughout the mucosa and close to the anus were mucosal defects measuring up to 3 mm. which extended into the subcucosa. Also seen were single ridges about 20 mm. from the anus. Throughout, the mucosa was thickened by many fibrous bands.

Microscopic examination of the rectum showed the mucosa to have been completely replaced by a very cellular granulation tissue from which infiltrations extended into the muscularis and to the outer layer of the rectal wall. The granulations were composed of large mononuclear cells, lymphocytes, plasma cells and occasional single polymorphonuclear leucocytes. On the inner surface there was a thin layer of structureless necrotic tissue. The ulcer in the ileum resembled the ulcerative lesions described in the rectum.

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Hemorrhoids: Their Origin and Treatment*

By

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UNDER the general heading of hemorrhoids or "piles," the layman groups certain conditions causing itching, pain, bleeding or purulent discharge in the region of the anus. Unfortunately, many patients and some doctors proceed at once to therapy without examination. So it comes about that of the cases of rectal cancer reaching the larger clinics, 1/3 have had recent treatment—often surgical—for hemorrhoids. The "Golden Rule of Proctology" is *examination*—thorough and if necessary, repeated examination—even under anaesthesia.

Granted, then, that adequate examination has revealed the presence of hemorrhoids, we may consider the conditions properly grouped under this inclusive term.

External hemorrhoids are varicosities of the inferior hemorrhoidal vessels. They are subcutaneous and sensate.

Internal hemorrhoids are varicosities of the superior hemorrhoidal veins. They are sub-mucosal and insensate.

"Mixed piles" are composed of external and internal hemorrhoids and have all the attributes of both.

A great deal has been written about the *causes of hemorrhoids* but, in fact, they follow the Mendelian Laws. They are exactly the same as varicose veins in any part of the body. The pathology of their formation is as follows: Some degree of stasis is prone to occur in the long column of blood extending from the rectum to the liver especially since these veins have no valves. This leads to a local rise in venous pressure with increased CO_2 and decreased O_2 which, together with the sluggish removal of toxins, tends to injure the musculature of the vein. Should this condition continue, the muscle cells will soon be replaced by fibrous tissue. The occurrence of any great stress or strain or even the persistence of lesser ones will cause these weakened walls to become stretched and tortuous.

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Submitted June 1, 1934.



Fig. 1. Strangulated hemorrhoid.

In short, many of the so-called causes of piles are merely the precipitating or trigger factors which, acting upon poor-grade physiology, convert it to pathology.

Internal hemorrhoids may be prolapsed at defecation to return spontaneously or be reduced manually or they may remain chronically prolapsed. Thrombophlebitis may be present causing prolapse, swelling and pain. Gangrene and ulceration can occur or fibrosis and pseudo-polyp formation may be a late stage. Other conditions such as fissure, abscess or fistula may complicate hemorrhoids and require appropriate treatment. It follows that there is no single method applicable to the variety of conditions grouped by the layman under the heading, "piles." The following outline of treatment has proved satisfactory. *It must be remembered that the principles of surgery are alike, wherever throughout the body, one operates.*

1. EXTERNAL HEMORRHOIDS

(1) Skin tags are satisfactorily treated by subjacent infiltration with ½% novocain and or anucaine and removal with scissors in such a manner that the wound is oval and radial to the anus, continuing beyond the corrugations. Small bleeding vessels are briefly compressed by forceps, and tied, if necessary. A pressure dressing is applied and held firmly by a T-binder. The wound heals by granulation. If many tags are present there is a choice of removal at one sitting at the hospital or one at a time at weekly office visits.

(2) Thrombotic external pile or marginal subcutaneous clot is found usually at the right or left of the anus and rarely at the commisures. The etiology is somewhat obscure but considerable percentage is associated with some type of effort. There are two varieties: the single, large clot which is extravascular and the cluster of small "bird shot" which may or may not be within the lumen of the veins. Rarely, an external pile of this type is continued into a thrombosed internal hemorrhoid.

In the common, external variety, under local anesthesia with ½% novocain and anucaine, an oval of skin corresponding in size with the lump—its long axis radial to the anus—is removed with the subjacent clot. In the "bird shot" type, a similar oval of skin is excised and all the clots readily are removed with the help of pressure and bleeders are tied: packing the wound with a narrow gauze-strip, removed in 24 hours gives excellent results also. A pressure-pad with firm T-binder is applied and is removed next day. The patient continues at his occupation and merely requires supervision of the wound. The removal of an adequate oval of skin is followed by a linear scar and obviates the disagreeable tag following healing when other operative procedures are employed. In the rare cases where the external clot forms but a part of an extero-internal thrombosed hemorrhoid which extends upward several centimeters from the anal margin, the operation will be of the type described below under the surgical treatment of internal hemorrhoids.

II. INTERNAL HEMORRHOIDS

Injection treatment is indicated only for internal hemorrhoids.

The purpose of the injection is to promote fibrosis and contraction of the varicose vein and its mucosal covering. Therefore the most suitable type is the simple uncomplicated pile filled with blood. The most un-responsive ones are the fibrous, meaty types for success merely changes the characteristics of the tumor.

Injection of infected or ulcerated piles may be actually dangerous.

Patients' prejudices frequently force the use of injection treatment in some unsuitable cases, but skill-



Fig. 2. Marked prolapsing hemorrhoids.

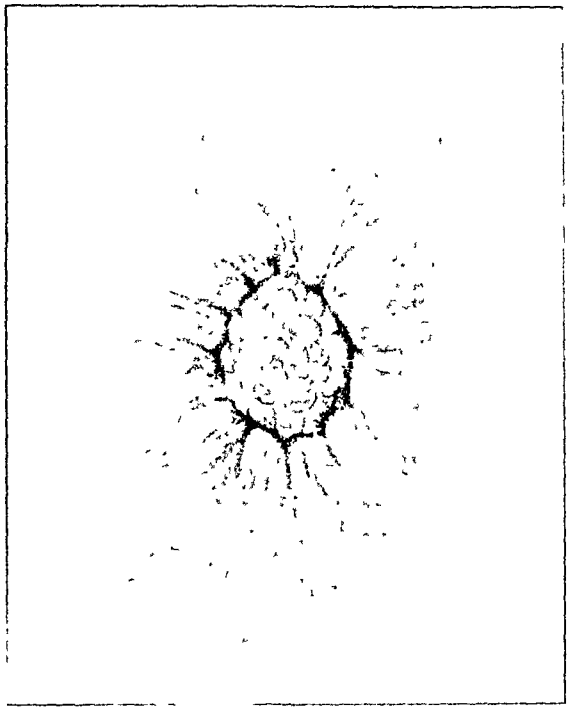


Fig. 3. The so-called strawberry internal hemorrhoid. This is the type of hemorrhoid which bleeds profusely.

ful technic permits the method to be of some benefit even if only temporarily.

Long experience has convinced us that, in our hands, 5% phenol in almond oil is the selerosing agent of choice.

The site of the injection is 2 cm. above the pile and into the sub-mucosa. The position is proven if the point of the needle is freely moveable under the mucosa. Fluid should be injected until stria are obvious and blanching has commenced. Any resistance to the introduction of the needle is evidence of the presence of existing fibrosis and contraindicates the treatment. If the hemorrhoid is polypoid, a small amount of 15% phenol in almond oil may be injected into the stalk in an attempt to cause it to contract.

The position of the patient is optional but we prefer that of Hanes'. Injections are usually given singly and at weekly intervals.

It is unfortunately true that injection is a more delicate procedure than is hemorrhoidectomy, and if improperly performed may have disastrous consequences. Therefore, it is evident that those intending to practice the injection treatment should be well equipped with the necessary instruments and solutions and should have learned the technique from an expert in the procedure.

The first injection nearly always stops bleeding or prolapse and succeeding injections usually are without incident. A series of indurations can be palpated in ring-fashion well above the anal margin in properly performed injections; endoscopic examination will reveal the presence or absence of soft, redundant tissue. If there is no evident hemorrhoidal tissue and no symptoms, the patient should be dismissed with instructions to return for a check-up in three months.

The advantages of the injection method are the absence of pain, loss of time from business, treatment is carried out in the office and there is no "operation" in the lay sense of the term. The disadvantages are the possible occurrence of sloughing or severe hemorrhage. Slough is certainly avoided by the correct placement of the injection solution; by so doing, also hemorrhage is minimized as it does not occur in the absence of slough. We encountered one unusual complication: following a single correctly-placed injection of 2 c.c. phenol (5%) in almond oil; there was a marked swelling of the rectum and recto-sigmoid accompanied by tenesmus, mild obstruction symptoms, slight pyrexia and moderate leucocytosis; there was no bleeding or discharge; endoscopic examination showed a swollen, pale, glassy mucosa somewhat resembling "bullous edema" of the bladder as seen through the cystoscope. The condition subsided in a week and was followed by obliteration of the internal hemorrhoids.

A recurrence of true hemorrhoids is found in over 10% of cases treated by injection therapy and formation of prolapsing fibrous polyps is even more frequent.

Operative treatment of hemorrhoids is more or less standardized today, the common operations being ligature and excision for ordinary piles and the clamp, excision and ligature technic in the case of large meaty ones.

Full descriptions of these technics are as follows:

Two ounces of castor oil are given 36 hours preoperatively and a cleansing enema of starch is administered at least 12 hours before operation.

We prefer to use ½% novocaine and anucaine infiltration as anaesthesia.

Any complications such as fissure, polyp, or spastic hypertrophied sphincter can be dealt with at the time of operation.

Either the left Sims' or the lithotomy position give excellent exposure.

The perianal region and anus are well painted with any of the usual antiseptic solutions and the area draped. Slight traction with the fingers on the perianal region will allow the lowest portion of each hemorrhoid to be brought into view. A curved hemostat (Kelly clamp) is introduced into the anal canal, opened and placed astride each pile, in turn, but in such a fashion that no skin is caught when the clamp is closed. Traction now is made on the clamps and the piles and the canal can be inspected. Any one clamp is selected and raised up and towards the midline;

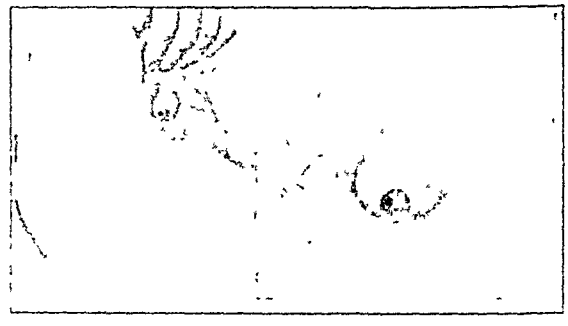


Fig. 4. Thrombotic hemorrhoid. (Reproduction from a photograph).

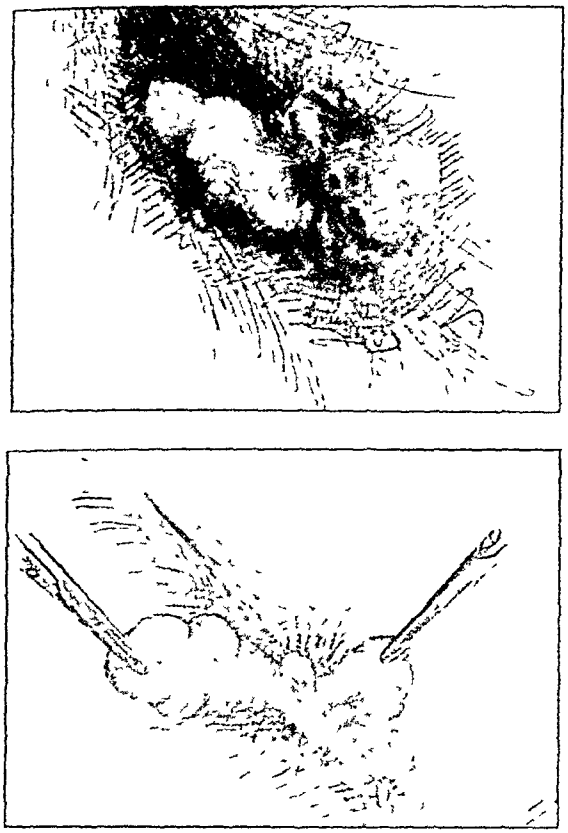


Fig. 5. Fibroid tumors of the rectum following the injection treatment for hemorrhoids.

the muco-cutaneous junction is thereby exposed and divided with scissors transversely over a distance corresponding to the breadth of the pile. The clamp now is taken in the operator's left hand and pulled up and out exposing its tip; a round-bodied, curved needle carrying a strong linen or silk thread, then transfixes the pile a short distance below the clamp-tip, the needle is removed and the thread is firmly tied proximally and then both ends are brought out, one on each side of the clamp and again tied, the ligature thus being made to lie in the raw area previously produced by scissors cut at the muco-cutaneous junction. The pile is excised leaving a generous stump. The other piles are treated in a similar manner; the area is carefully inspected for any bleeding point, the clamps are removed separately and the stumps are permitted to drop back into the rectum.

In the clamp excision and ligature technic, a heavy hemorrhoidal clamp is affixed as above. The cephalad portion of the mucous membrane with its vessels is transfixed and ligatured. The clamp is over-sewn with a running suture and slowly removed, and while the suture is tightened, leaving a linear wound.

External tags now are snipped off and any other conditions demanding attention are dealt with. A spastic hypertrophied sphincter associated with fissure is treated by division by knife in the posterior commissure. Lastly, the index finger is passed through the canal to make sure that no "diaphragm" was made during the operation. Dressings are applied to the anus and perianal region in the form of an inverted pyramid; small pads over anus, covered by pads of gradually increasing size. A large pad and a T-binder are firmly applied. Following operation, a sedative may be required for sleep on the first night but rarely thereafter.

After-care is of the simplest. Usually the dressing is changed after 48 hours and following each bowel movement. If there is unusual delay in moving the bowels, several ounces of warm olive oil are placed in the rectum and allowed to remain there over night. If spontaneous evacuation does not then occur, a simple enema is given through a catheter. Sitz baths may be employed with advantages from the third day on. The patient sits up in bed or chair usually on the third day or the fourth and may leave the hospital 24 hours later. The ligatures usually come away 8 to 10 days after operation and without pain. At this time a digital examination is made so that the surgeon may be certain no "diaphragm" has formed. The olive oil instillations gradually are diminished and finally omitted. Four weeks after operation, the anus and canal present a normal appearance; evidences of operation are minimal or absent.

It will be noticed that in the method outlined above, the sphincter is not stretched, the mucosa is not dissected up or stitched, there is a minimal amount of ligation of bleeding points, external tags are separately dealt with, skin wounds are not sutured, no special instruments are used and no tubes, plugs or drains are placed in the anal canal. Recurrences are uncommon: in our experience, less than one per cent.

Since we have perfected our technic of anaesthesia with ½% novocaine and anucaine, we have performed a large number of hemorrhoidectomies in the office with uniformly good results. Our technic varies in no wise from that employed in the operating room except that the Hanes' position is preferred. Since our anaesthesia can be made to last as many days as desired, we are under no obligation to skimp our surgery. The full operation is performed at one sitting. The patient is sent home to bed and returns for inspection in 48 hours. No sedatives are needed and the patient is able to carry on his work after the first visit.

One patient, a traffic policeman, contrary to our instructions, returned at once to duty and experienced no pain whatsoever.

Note: We cannot express too highly our gratitude to Dr. R. V. Gorsch for this anaesthetic which has opened up an entirely new field of operative proctology.

SUMMARY

External and extero-internal hemorrhoids are treated by surgery only.

Internal hemorrhoids may be injected or excised.

Hemorrhoidectomies may be performed in the hospital or the office.

Contrary to our youthful statements, all manner of plugs and tubes are contra-indicated in hemorrhoidectomy.

The Significance of the Icterus Index in Proctological Disorders

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THIS preliminary communication is designed to emphasize the significance of icterus index in rectal disease, as distinguished from the worth of the estimation in hepatic or hemolytic disorders. We desired to determine its value, if any, as a diagnostic test indicative of the presence or absence of infection harbored in the rectum and adjacent structures; also whether, by this test, the severity and chronicity of rectal lesions can be determined. In short, is increase in the icterus index in proportion to the severity of the infection and does it return to normal with the eradication and healing of the lesion? Such a determination would be of great value to the proctologist, especially in certain clinical entities whose etiology is either diverse or unknown; for instance, pruritis ani. A fairly exhaustive search of the literature fails to reveal any investigation along the lines embodied in this paper.

Our incentive for this study came about accidentally. In the routine blood report of a case of pruritis ani, we noted that the icterus index was above the normal level although clinically there was no evidence of disorder of the liver or blood. A repetition of the test in many other patients with the same condition showed uniformly high results. An unselected series of patients from Dr. Frank Yeoman's clinic at the Polyclinic Medical School and Hospital then was subjected to the test and again in the majority of those with anorectal disease there was a concentration of bile pigment higher than the accepted standard.

The term *icterus index* is used merely to express the degree of yellow color imparted to the blood by the bile pigment, bilirubin. Briefly stated, bilirubin is an intermediary substance formed by the liver from the food, the body cells, and the liberated hemoglobin, and excreted from the blood. When it reaches the intestine, the bilirubin in the bile is broken down by the action of intestinal bacteria and forms urobilin, which is responsible for the brown coloration of the stool. Not all of the bilirubin is thus destroyed; some of it is reabsorbed into the blood, giving the serum a yellow color. The icterus index measures the intensity of color which this bile pigment imparts to the serum. The liver, however, is not the only source of bile pigment; it is produced independently by the reticulo-endothelial system (spleen, bone marrow or blood vessels) (1). Bilirubin from the latter source, however, is also excreted through the liver from the blood.

It is stated (2) that the normal figure for the icterus index (the intensity of the yellow color imparted by the bilirubin to the blood in the absence of hepatic or hemolytic disease) lies between 3 and 5. The increase of this pigment to 6-15 is claimed to denote latent jaundice, and at and above 15 the clinical symptoms (yellow color of skin and conjunctiva) are apparent. Carotene sometimes, although rarely, must be taken into consideration but is omitted from this discussion.

Heretofore the concentration of bilirubin in the blood has been of value chiefly in determining the severity of jaundice produced by excessive hemolysis of red cells from any cause, and loss of function of the liver cells from toxic or obstructive lesions. In either case the liver was unable to excrete bile (bilirubin) into the intestine, with the result that it was retained in the blood, causing clinical jaundice. Occasionally also it was used to determine the effect of arsenicals on the treatment of syphilis. This point is stressed because, to the best of our knowledge, none of our patients showed any clinical signs of the above mentioned disorders.

To explain the increase of bile pigment shown by the icterus index in our studies we offer tentatively the following theories. We believe that infection involving the vascular bed (phlebitis?) of the rectum or lower colon is carried by lymphatic extension to the liver, producing a hepatitis sufficient to interfere with the pigment excretory function of the liver (latent infectious jaundice). Another explanation is that the excess bilirubin is formed by the reticulo-endothelial system, chiefly the vessels of the hemorrhoidal plexus. It is generally conceded that these cells are strongly phagocytic and have much to do with the breakdown of the hemoglobin into bilirubin. This may be explained on the basis of the great proliferative capacity of the cells of the reticulo-endothelial system.

We are not prepared to state, as yet, whether this condition is confined principally to the vessels of the hemorrhoidal plexus following infection. Whatever the cause of this oversecretion of bilirubin, the liver is apparently unable to excrete the excess as shown by an icterus index above the normal.

One more point to be clarified is the value of the icterus index as a means of determining the amount of bilirubin in the blood. On this subject the literature reveals that opinion is by no means unanimous. Some reports seem to show that the quantitative van den Bergh test is considered more reliable; we report a few such tests. Ottenberg (3), however, maintains that the icterus index is more accurate in determining the level of the blood bilirubin and also its variation from day to day, which is even more important. For

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this reason, and on account of its simplicity, he prefers it to the van den Bergh test.

A summary of our findings returned from estimating the icterus index in patients with proctologic ailments, shows it to be above the normal: in 16 (87%) of patients with pruritis ani, mostly of the third degree; in 7 of 9 patients (80%) with internal hemorrhoids accompanied by various degrees of infection, ulceration and prolapse; in all of eight with fistula in ano; in 5 of 9 patients (55%) with fissure in ano five (55%); in 4 of 6 patients (75%) affected with external thrombatic hemorrhoids.

Of the total of 52 cases studied, 40 exhibited an icterus index well above the accepted normal figures; that is, of an unselected consecutive group of rectal disorders, 81% revealed abnormal figures in patients who clinically gave no evidence of disease of the biliary or hematopoietic system. (Twenty-one patients were omitted from this series because the rectal findings were too diverse to be classified into groups, but of these the majority gave abnormal icterus index readings).

The tests all were performed by one individual, an experienced technician in the hospital laboratory, thus obviating the chance of personal error. The technician did not know the purpose of the tests or the clinical findings in the patients referred to him.

One of our many future problems is the matter of control with normal patients whose anorectal apparatus has been thoroughly examined and the foci of infection excluded. Other measures will include a thorough medical examination to exclude disorders of the blood from causes other than the biliary system; determination of bilirubin, blood cholesterol and sedimentation rate; and liver function tests with intravenous Azorubin S with recovery of the dye by means of an intra-duodenal tube according to the method perfected by Dr. Samuel Weiss (4, 5, 6) in the Gastroenterological Clinic of the Polyclinic Medical School and Hospital.

CONCLUSIONS

We wish to emphasize that in this report our purpose is merely to indicate that a large percentage of patients with rectal infections reveal an icterus index above the accepted normal (generally considered as 3 mgm. per 100 c.c. of blood).

We hope to carry on this work in more detail and reach a definite conclusion for or against the value of this test in proctological disorders. In the past, practically all the work along this line has presupposed the presence of disease of the hematopoietic and biliary systems without consideration of other cause for an increase in the serum bilirubin.

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SECTION VIII—*Editorial*

NOTE: The editorial contributions published in this Journal represent only the opinions of their writers. Such being the case, this Journal or the American Gastro-enterological Association is in no way responsible for editorial expressions.

CONCERNING THE ENIGMA, PEPTIC ULCER

(Continued from the September, 1936 issue)

B. *Therapy limited by the nature of ulcer pathology.* From the previous discussion, it would seem that, in respect gastric ulcer, non-surgical treatment confronts the problem of managing a *mucosal* defect in not more than 20% of patients, taken consecutively of a group which had symptoms and signs so urgent as to warrant surgery. It may be stated, that often such mucosal lesions are transient; they represent but stages in tissue defense and repair.

Our observations on groups of gastric ulcers exhibiting mucosal defects which did *not* go on to surgical intervention, indicate that whether or not they were treated, each ulcer possesses a pathologic life-cycle, highly individual in character. Often, the mucosal defect heals itself in strikingly short time. If one is to place any reliance upon the "acid-response" test suggested by W. Palmer, and improved by Hardy, in even extensive lesions, mucosal epithelialization may occur in 24-36 hours. But although occult blood may be absent from the gastric content and free HCl and pepsin be "normal" when there has taken place complete epithelial repair, the patient's symptoms rarely disappear unless gastric peristalsis is absent or at a minimum rate or degree of intensity. In such circumstances, it becomes evident that pain, as well as other symptoms, are due not to the "corrosive action" of gastric juice, to hyper-pepsia or to foods which locally "irritate" the "ulcer," but they depend upon excitation of mural reactions at the site of the pathology in the wall. We have observed instances where large, blood-seeping, mucosal areas existed and the gastric content was abundantly rich in acid and pepsin, but cessation of peristalsis, upon rectal feeding or the exhibition of antispasmodic drugs, was followed by complete clinical comfort.

Of the remaining ulcers of the group being discussed in this communication, (80% of the group total) *i.e.* lesions not presenting the mucosal *facade* so generally thought of as concomitant with this gastric affection, the actual therapeutic problem was the management of *mural* pathology of variable and varying extent, ranging from more or less complete attempts at plaque-like, scar-formation to roughly, wedge-shaped areas; in general the base of the wedge lay toward the submucosal tissue. Pathologically, these wedge-shaped areas exhibited destruction of normal, mural structures side by side with disordered blood—and lymph—stream architecture, and early or late attempts at the fibroblastic proliferation of repair. Such pathologic foci most commonly were confined within the stomach walls but, as mentioned above, frequently enough, they penetrated to and included the serosa

("soldier-spot" lesion); in a number of cases, neighborhood structures were involved; in a few instances, there was "perforation"; when such occurred, there was a *serosal "ulcer facade"* to the lesion; the "ulcer's" base then was formed by the submucosa. If one may judge from the literature, considering gastric "ulcer" as having its "open" aspect at the *serosal* surface of the stomach's wall, is a novel conception, certainly with respect non-surgical therapy. However, such condition not infrequently is the finding. It is quite as legitimate to regard "ulceration" as occurring at the serosa as at the mucosa—and certainly is warranted by the facts. One's view-point only requires changing from that which some seventy years have established as a "tradition" in respect "peptic ulcer." Our study of a representative group of operatively proved ulcers, demonstrates that, in 4 of 5 such, the progression of the initial mural pathology is *towards the serosa* and not *towards the mucosa*. The mucosal involvement definitely is a pathologic accident; it is a complication during the development, and, the attempts at repair, of the mural focus, when submucosal and then mucosal tissue-nourishment is interferred with. It is evident that the mucosal "ulcer"-aspect of gastric ulcer does not begin, and is only secondarily maintained, as a consequence of chemical action or food traumata. Just as ulcers present on the endocardium, in bacterial endocarditis, later do not produce the mural myocardial plaques which the heart exhibits as "soldier-spot" defects, at places where there has been localized, myocardial destruction and subsequent repair by scar, so gastric ulcer, initially, does not begin as *mucosal death* from intra-gastric causes and the mural pathology does not appear as a consequence of what has occurred in the mucosa. *The mural lesion is the primary malfunction;* from that, depending upon its nature and extent, arises the so-hastily named "peptic" mucosal defect of ulcer-form.

While many constitutional, metabolic, toxic, bacterial or neuro-psychic agents or mechanisms may be responsible for initiating the mural lesion, evidence is strong that their action is exerted through the blood and lymph vessels in the stomach wall. It is evident that some mural lesions occur as a consequence of *arterial, arteriole* or *arteriole-capillary occlusion* (sclerosis, plugging by clot, rupture, prolonged spasm); others represent *venous stasis* prolonged to a degree sufficient to stop blood-flow; *lymph stasis* likewise may be so complete that tissue catastrophe may follow when this "third," and little considered circulation, no longer is possible. Bacterial deposits can be considered "accidental" or secondary in the great majority of gastric ulcers. Future studies made with the object definitely of analyzing the minute pathology of peptic ulcer may enable us to distinguish the various ulcers in relation to the nature of circulatory block; such studies, strangely, rarely have been made. It is more than likely that, depending upon the nature of the initial circulatory interference (arterial, venous, lymphatic) ulcers vary as to clinical course. A phase of ulcer observation in regard to etiology, should be the careful study of the capillary circulatory bed and observations on the general lymphatic state. Certainly, such ulcers as have a tendency to early and free bleeding would appear to depend for their initial mural pathology upon arteriole rupture. The seeping ulcer of the patient with external or constitutional evidences of a tendency to prominent veins and venous stagnation, may arise from local, venous stasis; such ulcer seems to run a course relatively free from the acute, sudden, copious hemorrhage-accidents common to those in which arteriole blood-flow is at fault.

C. *The Effect of Ulcer Development, Extension and Repair Upon Gastric Function as Related to Treatment.* Not often does non-surgical ulcer management as practiced concern itself with any consideration of at what stage of healing may be the ulcer. The patient is *fitted* to such "standard" regimen as that on which the clinician has been "sold," irrespective of whether mucosal epithelialization has or has not already occurred, or a mural lesion is progressing towards the serosa, or a tough scar deforms the stomach's contour or blocks considerable of the pyloric channel, or a crater-diverticulum interferes with orderly peristaltic function or a recent hemorrhage, (in association with arteriosclerosis and actual or potential hypertension) has given warning of impending and probably fatal bleeding or perforation. Almost universally, the same kind of management is exhibited as when the only lesion exists is a mucous "erosion" quite capable of healing itself if allowed to. Pathologic considerations all too frequently give way to those rule-of-thumb therapeutics which were proposed many years before exploratory surgery and examination of pathologic tissue were possible. And, even though responsible evidence proves that, in peptic ulcers unassociated with gastric stagnation, the titre of gastric juice does not exceed a vaguely theoretic "normal," the vast preponderence of "treatments" has, as its basic idea, the "neutralization" of free HCl so that "corrosion" of the ulcer area may cease. (Who, indeed, is able to say what degree of gastric acidity *is* or *is not* "normal" in health or disease, for any given subject? Studies of individuals absolutely free from dyspepsia, have returned acidity readings far higher than those recorded for patients with proved ulcers; observations after psychic, emotional or physical effort have recorded acidities exhibiting extraordinary increase; lastly, it is admitted generally, that our laboratory methods for estimating acid values are wide open to criticism).

Of the series of ulcers being discussed, where symptoms were so distressing as to warrant dangerous surgery, in not 20% was epithelial protection lacking at the ulcer site. It is but pertinent to ask, what effect upon mural defects, now quiescent and again progressive, could ant-acid therapy exert? Apart from a diet of limited quantity which permits periods of gastric peristaltic quiescence, lavage which has a similar effect and bed-rest which favors circulatory equalization, medicinal agents as *positive* healing substances, are not far from being of about as much significance as is the reading "page 123" of the christian (?) science (?) "Manual," the ground bark, dried snake-skin and powdered guano mixture of the can-canning, South Sea Island Medicine man or the flashing colored lights and the mystic whirl and buzz of the machines devised (certainly, with a sardonic chuckle at "what fools, etc.) by the late Abrams out in the exhilerating and reason-shaking air of ever-curious California. Just as it is the present vogue to ascribe the pathologic mural changes which precede the development of the mucosal lesion of ulcer, to "emotional instability," the "kinetic drive," the result of "stress and strain of modern living" and the like, so, in the non-surgical attack upon ulcer, it appears that much in our aramentarium depends for its

efficacy upon the psychic effects of the routine established: the taking of "*this* at 8 and *that* at 10" and the consolation which may be brought by impressive and solicitous physicians—not forgetting the ministrations of nurses who well know how to cojole and to swish their crinoline. That these observations are warranted is demonstrated by the recent experiments of Flood and Mullins (*Am. Jour. Dig. Dis. and Nutrit.*, Vol. III, No. 5, July, 1936, p. 303): hypodermatic injections of sterile salt solution proved quite potent to assuage pain and discomfort; quite as potent as an expensive and widely popularized "research" preparation or of even commonly used drugs and limited diet. Such experiments certainly should compel serious thinking among physicians, particularly among gastroenterologists. They should lessen the temptation to fit patients to "standard" routines of treatment; they should emphasize the fact that, in 80% of proved ulcers, epithelial protection already has been accomplished through "natural" reparative effort; they should lead to a strict scrutiny of what, pathologically considered, in *each* ulcer subject, actually is to be treated; they should bring support to the opinion that whenever — by whatever safe agencies — the motor function of the stomach can be controlled to a degree that one controls the movements of a fractured leg-bone to secure union, so, proportionally, there is given the greatest opportunity for the normal healing of gastric lesions. Surgeons are familiar with such facts: after extensive gastric surgery, they keep stomachs free of all foods and drugs for several days. We have examined a number of stomachs which have been subjected to operations, when the patients have died from exhaustion, embolus, etc. As early as 27 hours after major surgery, we have observed such complete epitheliazation of great areas of the mucosa that, aside from support to muscle coats, there was no need for stitches to prevent gastric leakage.

D. *Gastritis and Gastric Ulcer.* Fortunate it is, that many so-called "ulcer" patients are non-surgically managed for only mucosal "erosions" or various types of "*gastritis.*" While the whole subject of what constitutes *true gastritis* is in flux, yet it can be said that in none of the vaguely delimited "types" of gastritis has it been shown that such lesions lead to or favors the development of true gastric ulcer. In other words, as has been emphasized above, however great may be the departures from the normal in mucosa or submucosa in the conditions loosely grouped as "gastritis," unless such be accompanied by a localized *mural* defect, classical peptic ulcer does not supervene. Even in those instances of localized or general infectious or suppurative "gastritis" (a rare occurrance) abscess-like formations are not followed by any lesion even suggestive for gastric ulcer in gastroscopic or roentgen appearance, in clinical course or termination. *Initial mucosal lesions tend to remain mucosal* or *submucosal;* they tend to heal without distinct *mural* pathology such as one finds in true ulcer. A suggestive distinction is possible: in instances of local, severe, traumata by intragastric burns (cauterization, hot fluids and the like), the resultant damage rarely penetrates the submucosa; it tends to heal rapidly and completely; on the other hand, when severe body-surface burns occur and gastric ulcer, frequently of hemorrhagic type appears, the lesion heals slowly. In such circumstances, pathologic studies reveal true mural lesions such as accompany peptic ulcer of etiology other than body-surface burns. One may note localized or multiple mural areas, in which arterial (perhaps venous or lymphatic?) circulation is interrupted by emboli, by capillary rupture and extravasation of blood; the tissues, lumen-ward, then necrose, are digested by any proteolytic agent present (gastric juice, regurgitated duodeno-jejunal secretions, bacteria or even the peptid-splitting enzyme normally present in the blood serum itself (Smithies, F., "A Peptid-splitting Enzyme in Normal Blood Serum, *N. Y. Med. Jour.*, 1913, 98:619). In many instances of "gastritis" accompanying gastric ulcer, the so-called "gastritis" represents little more than local or general variations in submucosal or mucosal blood-flow, combined with such secondary anomalies as arise when epithelial structures are endeavoring to preserve themselves and to continue functioning. Such being the case, one ceases to wonder at the so-frequently changing pictures of "gastritis"; certainly, recognition of these basic facts should cause hesitation with respect attempting to construct any dependable classification—clinical or pathological—of types of gastritis. The evidence seems clear that gastritis is not a fore-runner of true peptic ulcer.

E. *The Chronic Ulcer with Extensive Scar Formation.* It should seem not necessary to emphasize that, with respect the scar-tough, deforming, obstructing or "penetrating" forms of mural lesion, whether or not such have lumenal *facades* of ulcer type, (unless the lesion has a luetic etiology) no drugs with which our profession is familiar can be introduced into the stomach and there be capable of exerting the slightest positive therapeutic effect. Not that gastric rest —motor and secretory—combined with lessening the work-load of the viscus and the exhibition of acid-neutralizing drugs may be not followed by improvement in the degree of the patient's physical comfort. It is common knowledge that patients do experience less distress on such regimen. However, it should be recognized and, frankly admitted, that such restoration of well-being does not mean that the mural pathology has been affected positively by the drugs given. Indeed, all clinicians have observed instances where most serious and lamentable "complications"—as gross or fatal hemorrhage, acute perforation—have occurred when patients were symptom-free. These dreaded happenings are all too-commonly recorded as intruding upon what appeared to be satisfactory treatment results.

Cessation of symptoms upon the exhibition of diet, rest and antacid drugs doubtless is due to the fact that the peptic ulcer lesion has a highly individual life-cycle. Initiation of the mural lesion, advancement of tissue destruction to include submucosa and mucosa, with resultant mucosal ulcer *facade,* follow an orderly course. The extent of tissue destruction depends upon the location, character, persistence and size of the mural defect. Tissue lysis and reparative efforts follow in a regular fashion; the endeavor ever is towards histologic repair, in kind or as fibrous scar. When patients are acutely affected—whether or not there is mucosal destruction—they seek medical or surgical aid. It follows that, provided tissue destruction does not give rise to copious hemorrhage or perforation of the stomach's wall, any therapy which brings "physiologic rest" (Smithies) to the viscus, aids the normal reparative effort such as is common in any lesion, anywhere, when structure is destroyed

and yet neighboring parts retain their native ability to heal. One need not emphasize how, in such circumstances, many forms of therapeutic procedure obtain vogues as being "specific." All clinicians are familiar with the "specific" therapy which, from time to time, has been advanced for the management of typhoid fever, pneumonia, liver cirrhosis, nephritis, myocarditis, with or without coronary disease. The common factors of usefulness in all the varied therapy of these affections have been those concerned with general care, rest, relief of symptoms, watchfulness. Particularly is the analogy between ulcer management and degenerative heart disease a close one. Just as in the sclerotic, vascular and myocardial affections do we observe relieveable, recurrent, acute episodes, so, in peptic ulcer, we observe mural pathology, now active now quiescent. In the active phases, there occurs stomach (or duodenal) dysfunction, relief of which is desirable; but symptom-relief actually is not positively *curative* towards the initial or the progressive mural pathology. Nor can one say that "recurrences" always mean that the original "ulcer" again recrudesces. The studies of Dr. Gregory Cole appear to indicate that "recurrence" often means the appearance of a new ulcer or the marginal extension of the initial lesion after the fashion in which the original ulcer arose. One sees the effects of similarly-acting pathologic sequences in hearts where myocardial destruction and repair are the consequences of vascular faults.

We have no quarrel with the various regimens exhibited in the management of gastric ulcer, provided the clinician has an honest appreciation of his limitations and those of the problem confronting him. Our stand is that the clinician should realize that relief of symptoms has little positive significance with respect the pathologic processes which are present in the stomach's wall. He should recognize that his therapeutic agents, (particularly drugs) except in instances of lues, have no "specific" or direct action. Thinking pathologically, not chemically, grouping his patients on the basis of probable mural pathology present in the individual, ever bearing in mind the significance, upon function and visceral integrity of pathologic anomalies murally located — all such considerations will result in less loose thinking, less faddism, less waste of effort in searching for "specific" cures, and on individualization of therapy according to the gross and microscopic nature of lesion and the constitutional type of patient. So too, will it become evident that there should be a continuous form of management, *between acute episodes*, whose supervision may prevent or anticipate future incapacitation or life-taking complications.

F. *"Ulcer-phobia"* dominates many hosts. It has a serious bearing upon ulcer healing, upon economic usefulness, upon life as a pleasant and to-be-desired experience. Knowledge of the nature of the mural pathology present in the individual gastric "ulcer," should enable the physician to maintain an optimistic attitude, an attitude which readily is conveyed to patients. Barely 10% of peptic ulcers are associated with crucial crises. Surely, possessed of such knowledge, both patient and physician better can face the future. The serious complications demand early surgery. At the hands of qualified surgeons, the operative mortality, approximately, is 3%, when even the most aggravated lesions are included. The post-operative digestive morbidity is not 10%; this is becoming reduced as surgeons select their operative procedures to fit each ulcer and do not fit all types of ulcer to a rule-of-thumb procedure as is now, alas, so common in "medical" management. Only thoroughly competent surgeons—skilled in pathology as well as in technical manoeuvres — should perform operations upon the stomach: the "venturing" of the improperly trained has no place in visceral surgery. So, too, the non-surgical management should be in competent hands. Undoubtedly, at present, many functional gastric affections are being treated as ulcers, thus greatly adding uncertainty to statistics regarding "cure." In the presence of real ulcer, simply knowing the "steps" of a popular mode of management, does not justify the practitioner who has not a sound medical or gastro-enterological training in taking charge of patients. That this is so, is proved daily in any important clinic, by observing the serious situations which arise from hemorrhage or perforation during the course of fit-the-patient-to-a-formula types of managements. While there has been undue alarm over malignancy and its relation to benign, chronic, gastric ulcer, clinicians of experience, nevertheless, all too-often, observe patients arrive at stages of inoperable cancer during medical management by so-called "standard" forms of treatment. When the physician is treating accurately proved gastric ulcer, his attitude ever should be critical. Relief of distress, while a happy event to the patient, should not lull to apathy the medical attendant. By all means available —physical examination, laboratory studies, roentgen observation, gastroscopy—he should endeavor to secure unbiased knowledge not alone as to epithelialization of the lumenal ulcer-*facade* but as to the changing status of the primary, mural lesion. *This demands appraisal of the patient who has the ulcer even more than treatment of the ulcer itself.*

Frank Smithies, Chicago.

INTRODUCING VOLUME IV

THE *American Journal of Digestive Diseases and Nutrition* completes its third year with the current issue. During the past twelve months, numerous readers have given the Supervising Editor valuable criticism. The front page title is to be cast in a simpler type; this probably will appeal to most readers. All "section" divisions are to be done away with, except Editorial, Book Review and "The Clinic," so that major contributions will run in undisturbed sequence. About one-third of our correspondents wanted the page-size of the Journal somewhat reduced, but since such a reduction would interfere with the mechanical requirements for advertisements (a feature of essential importance to the Journal's survival) it has been decided to maintain the present distinctive format, especially because most readers actually like it. Taking our cue from the Journal of the American Medical Association, an attempt is being made to interest some advertiser in a front cover position, as has been suggested by many readers.

Generally speaking, excellent progress has been made by the Publishers, although, as yet, no reduction of their deficit has been found possible. The Publishers are holding an ideal before them and are trusting to the essential merits of the publication for its growth. As with the Editorial Council, so with the

Publishers, the motivation is the production of a clear-cut, serviceable archive in a special field, and there can be no doubt now of the permanency of the undertaking. No apology is offered, however, for exhortation to our readers to form the habit of making proselytes: we need greater circulation of the right kind; but the Publishers will not employ high-pressure sales' methods to secure such.

Manuscripts of increasing importance and quality continue to flow in from distinguished clinicians and investigators. Reprints are being furnished at cost to authors. Advertisers claim to be receiving unusually good returns from their accounts, due, no doubt, to the fact that the *Journal* is read largely by men in "key positions" in the profession, and men who recognize the *Journal's* sincere obligations to the firms who advertise in this periodical. The extremely high renewal percentage by subscribers indicates that the *American Journal of Digestive Diseases and Nutrition* already has become a "family affair," nay almost an institution in America.

While ground for gratification at present exists, we feel that there is much room for progress in all departments: constant refinement of format, contributions of still higher order, greater brevity by authors, even closer cooperation from readers than at present. In a very real sense the *Journal is yours.* We desire, and need, your complete cooperation as we launch the next (March) issue, Volume IV.

Beaumont S. Cornell, Fort Wayne.

SECTION IX—*Book Reviews*

(This section is open to contributions from any medical reader, whether or not a member of the Editorial Council).

"The Art of Ministering to the Sick," by Richard C. Cabot, M.D., and Russell L. Dicks, B.D. The MacMillan Company, 1936, 378 pages, price $3.00.

THE authors have written this book with the hope that it will be of interest to doctors, nurses, social workers, and to the sick themselves, as well as the ministers to whom it is addressed primarily. Each of the authors is chiefly responsible for certain chapters, whereas in several their ideas are intermingled so closely that one cannot tell which of them wrote the various paragraphs. This is somewhat confusing to the reader who frequently asks himself the question: "Who wrote this?" It is apparent, however, that the views of the two are in such complete harmony as to give the question little significance. An attempt has been made to follow a definite plan of organization, but it has succeeded rather poorly, due, perhaps, to the fact that the various aspects of the subject interweave so closely that it is difficult to separate them so clearly and sharply as would be desirable in an ideally analytical exposition. Nevertheless, regardless of its organization, the subject matter is valuable.

It is perhaps significant that it is addressed primarily to ministers, the authors obviously conceiving of the Christian minister as one who plays the role of an intimate friend and confidant rather than that of a formal high priest. It is rather surprising that so little has been written on this relationship between the pastor and his parishioners. The topic is a timely one and the book fills a real need, particularly as it deals with illness, death, and bereavement.

Recently an interest has developed in the provision of "clinical" training for theological students during the summer months between the terms of study. A description of this undertaking is included in the appendix and may be mentioned here because it illustrates the scope of the book. At present the agencies sponsoring such opportunities for clinical experience are the Council for the Clinical Training of Theological Students and the Earhart Foundation, both of which insist that the student be under the institutional supervision of some member of the medical staff and more particularly under the theological supervision of "an ordained minister who has had special training to prevent the student from being busied chiefly in social service or in medical, psychiatric or recreational activities, to hold him primarily to a study of his own professional responsibility and to instruct him in the resources of the Christian religion for meeting the needs which he sees." Both of these agencies are said by the authors "to be strongly opposed to the practice of psychiatry or to the use of psychoanalytic technique by the minister, although it is believed by members of both organizations that the minister has much to learn from the New Psychology. It is believed by the leaders of these two organizations that churches should not establish clinics for the mentally ill but should cooperate with other agencies to make the service given by the psychiatric clinics more fully available to the community."

The book opens with the question to be answered by it, namely: "Has the Protestant minister of today any good reason to visit the sick?" In the first chapter the three aims calling the minister to the sickroom are listed as "(1) to counteract the evils of specialism, (2) to give a devotion such as only religion can permanently inspire, (3) to care for the growth of souls." The first aim, that of counteracting the evils of specialism is made necessary, apparently, by the fact that modern doctors "lack the time, the interest, and the skill to make the social and spiritual diagnosis, or to give social and spiritual treatment to their patients." The authors concede that they would prefer to see doctors treat all of their patients' ills were it practically feasible for them to do so, rather than to turn over some of them to the nurse, social service worker, or minister. The ideal apparently is an all-around-man, such as Dr. Grenfell in Labrador. It must be admitted, in the opinion of the reviewer, that modern medical education does not produce and does not aim to produce this type of a doctor, for the emphasis is placed upon facts and objective data pertaining to the body, its organs and functions. On the other hand, all great physicians learn from experience the importance of these other factors, but in our present age of specialization we may perhaps agree,

therefore, with the statement attributed to Dr. James H. Means: "I believe the patient should send for his minister when he gets sick just as he sends for his doctor." The authors note some difficulty in attempting to delimit the precise sphere of the minister, but they succeed in making perfectly clear that it is one of assisting the physician, the nurse, the patient, and the family, of getting them all to work together under the supervision of the doctor for the good of the patient, and more particularly, that "it is the minister's duty to rouse the great energies, certainties, and faiths of the Christian religion." One's opinion of this goal will depend, of course, upon his own philosophy, but it must be conceded that for those who do accept the Christian faith, there is a definite opportunity and need of this type. For those who do not accept the Christian belief, there is still an opportunity, according to the authors, for the minister to be of definite assistance in helping the patient to develop the courage and hope with which to overcome the suffering and the inevitable ordeals of illness. There is ever an opportunity for the minister to inspire courage and "to devote himself to the growth of souls (in the broadest sense) at a time when pain, sorrow, frustration, and surprise bring experiences that invite a new start in life."

The chapters on preparation for such work emphasize the importance of personality and include pertinent advice with regard to one's conduct in the sick room. Medical students are inclined to look upon these attributes of the practitioner more or less derisively as the "bedside manner" or "personality" of the physician as opposed to his scientific knowledge. Dick points out that much of the important work of the world depends "upon personality not only in medicine but in all fields of human endeavor, that personality in the broad sense of the word includes knowledge, insight, skill, interest, hope, devotion." Adequate preparation is, therefore, essential. In the development of this subject Cabot has contributed two practical chapters dealing with the problems and difficulties likely to arise in the institutional care of the patient and the characteristics of doctors, their peculiarities, their points of strength and weakness.

In connection with the situation which the minister must face, Mr. Dick discusses at some length the conditions considered by him to be five forms of spiritual backsliding: loneliness, boredom, fear, bitterness and the morbid obsession of guilt." His approach to these problems is quite sane and applicable in the main to both the Christian and the non-Christian. Pain is divided into physical and mental suffering, the latter being less endurable than the former. While admitting that physical pain is almost always pure loss, four mental habits are suggested which may help us to escape bitterness and a loss of faith in a time of painful crisis: (1) Get beyond the childish impulse to place personal blame on some person or object for every difficulty or hurt. (2) Learn to see that nothing happens to you as a unique experience leveled at you alone by some special design. (3) Learn after each experience of pain to sum it up and discover what value you can wrest from it, and (4) Learn how evanescent pain is. Dr. Cabot is able to find real value in mental pain, however, for he sees it as an essential part of the growth process. The sense of growth or growth tension is seen as man's only real need on earth. "The sense of success and the sense of failure are signs that we are off the path of the growth process." When one is really on the path of growth "pain and pleasure, the awareness of success or of failure, die down to subordinate notes in the theme of growth." The meaning of the word "growth" is further amplified in the appendix, "growth as we use it connotes all that is morally good and all that is morally good must appear as growth. . . Growth takes place in character, not toward character; in wisdom, not toward it. There is no goal which we approach." Dr. Cabot's discussion of evil, of the problem of Job, is theological and is based upon his "fighting faith that there is an explanation for much that we cannot explain, that God permeates all with his plan, that "the universe must be under a plan, and that (that) plan could not be bad else it would contradict itself, as it seems to do in evil, and so be no plan at all." In the chapter on "Vis Medicatrix Dei" Dr. Cabot pays tribute to the healing power of nature, although he prefers to interpret the phrase as meaning the goodness of God. He then, in the following chapter, concludes the presentation of the situation with which the minister will be confronted by a series of brief but very pertinent comments on twenty-one different diseases and conditions, such as pulmonary tuberculosis, cancer, fractures, childbirth, adolescence, and insanity.

The third section deals with the primary needs of the minister in the practice of his art. It is felt that he needs a bag, like a doctor or a lawyer, which should contain "some Protestant equivalent for the Roman Catholic priest's stole, wafer, and oil," if there be such; a notebook, for the events of each ministerial visit should be noted, remembered, and to a certain extent planned just as are those of the physician's visit; small gifts and surprises, preferably loans, which will provide new trains of thought and leave fresh after-images for the patient's mind, and most important of all, perhaps, ideas for the mental kitbag must be packed, too. The authors emphasize the care which doctors and nurses should take in their prescription by literature, because patients have a high regard for their opinion and may be introduced inadvertently to an undesirable course of reading. The great importance, however, of a desirable reading program, as pointed out by Dr. Webb in his charming essay on "Prescription by Literature," is emphasized. Other types of occupational therapy, such as sewing, knitting, and various games, may often offer very satisfactory forms of diversion. In this section Dr. Cabot very ably discusses under the title "The Two Must Face a Third" the minister's relations with the sick, the danger of their dependence on him, and particularly the danger that women patients may fall in love with him. The last is admittedly difficult at times, but Dr. Cabot rejects the necessity of the "transference phenomenon," using the terminology of psychoanalysis, and feels that the situation can usually be avoided by the following precautions: (1) the maintenance of physical distance between the patient and the physician, or minister; (2) the avoidance of touch; (3) the presence of a third person whenever that is possible; and (4) *the implied presence of a third person*, thereby keeping the speech and action at all times entirely as it would be if a third person were present. The discussion of the needs of the

minister is closed with a brief section on the importance of "starting with the patient," taking into account his physical illness, the condition of his mind, his emotions, his spirit, and thereby establishing a satisfactory rapport with him. Good education should likewise start with the student, but Dr. Cabot notes that all too often it does not do so.

The section on methods, written chiefly by Mr. Dick, opens with a chapter on the lost art of listening, for the author feels that "if the Protestant church is to renew its contact and its interest in the care of souls, its leaders must descend from their pulpits and seek out those who are in need. And they must be prepared to listen." The listening must be creative in type, directed, leading the patient to think and talk about a definite subject. In directed listening the Christian minister is thought to make his nearest approach to the Catholic use of the confessional to which, above everything else, in the opinion of the authors, the strength of the Catholic church as an institution is to be attributed. Quietness is described as one of the methods for effective work in the sick room. This quality is desirable for any poised, healthy, happy life; it is peculiarly desirable in illness, but it is difficult to define exactly the technique of its use. In the well-written chapters on prayer and the use of scripture one is strongly reminded of the Gifford Lectures of William James on the "Varieties of Religious Experience." Prayer and the reading of scripture are important for the Christian if the minister is to fully "rouse the great" energies, certainties, and faiths of the Christian religion, but the authors do not recommend their infliction upon the non-Christian unless he so desires. The subject of note-writing is discussed and illustrated in considerable detail. Its importance seems obvious for any minister who takes seriously the task of visiting and aiding the sick. Two chapters by Dr. Cabot conclude the section on methods. The first deals with creative assertion, by which is meant the ability, difficult to define, to recognize heroism; the almost inspired ability to recognize the rare moments when one may, by the positive expression of "admiration, surprise and delight," reinforce or crystallize the patient's courage to the end that we may "build better than we know." The second chapter discusses the rituals of the sickroom, emphasizing the importance of a well-organized routine with one high point or climax daily. The day should be without quarrels or needless disappointments, and there should be moments of affection, or better still, a steady undertone of affection throughout.

The section on critical opportunities is devoted to preparation for an operation, to ministration to the dying, and to consolation of the bereaved. Mr. Dick devotes considerable space to his own experience with operations, because it is illustrative. He feels that the minister can do a great deal to prepare the patient psychologically for the operation, and that the best attitude for the patient to have is, "It is all right whatever happens." The importance of explaining carefully to the patient the result to be expected from the operation is emphasized . The ideal for the patient face to face with death is summed up by the authors in the words of a patient: "It is all right; whether I get well or whether I die—it is all right." Death is considered to be but an incident and the attainment of this point of view the final triumph of religion. The chapter contains a great deal of practical advice and philosophy, all leading to this thought, that "the tragedy or the victory of death is in the way one dies, not the fact of death itself." Dr. Cabot's excellent discussion of bereavement, giving further evidence of his deep insight into human nature, shows clearly that which consoles the bereaved and that which does not.

The appendix contains a number of stories of work with the sick, apparently taken chiefly from the notebook and experience of Mr. Dick. These notes and comments illustrating the importance of keeping a notebook and also many of the points discussed in the book add concreteness and precision to the various topics considered.

There are few who could not read this book with profit, although it probably will not appeal to the enthusiastic atheist, the confirmed sceptic, or the narrow-minded scientist. It should be most helpful to the minister. It should prove very valuable to nurses, social workers, medical students, the younger practitioners of medicine and even to many of those who have spent years in the practice of the healing art. It is a contribution toward the ideal expressed by Francis Peabody in the letter written to his friend and "scientific godfather," Joseph Pratt, at a time when he knew himself to be traveling in the valley of the shadow of death: "My great desire has been to have a medical clinic in which the highest type of scientific work was carried on in conjunction with the most human and sympathetic attitude toward the patients—a type of spiritual atmosphere which may be expressed by the word "Christian."

Walter L. Palmer, Chicago.

ABSTRACTS

CLINICAL MEDICINE

EUSTERMAN, GEORGE B.

Diagnostic Aspects of Roentgenologically Negative Gastric Disorders. J. A. M. A., Vol. 107, pp. 1432-1436, Oct. 31, 1936.

The efficiency of modern roentgenologic diagnosis permits classification of diseases of the stomach into roentgenologically positive and roentgenologically negative disorders. In recent years the radiologic diagnosis of gastrointestinal disorders has reached an accuracy of 90 to 95 per cent, although the exact nature of the lesion cannot always be successfully ascertained before microscopic examination. The conditions which are diagnosed by X-ray are gastric and duodenal ulcer, carcinoma, pyloric and duodenal obstruction and duodenal dilatation. It would also include gastritis and granulomatous lesions. Kirklin claims that about five per cent of all ulcers escape detection. The same may be said of small carcinomatous ulcers. Gastritis and small diaphragmatic herniae may also be overlooked at examination.

Gastric disturbances reflexly engend-

ered by disease of the abdominal viscera other than the stomach itself or its continuations exceed in importance the gastric neuroses, because of their nature and extent and the comparative frequency of their occurrence. They constitute from a third to two-fifths of all cases and include disease of the gall bladder, appendix, pancreas, liver, small bowel, colon, and such conditions as epigastric hernia and helminthiasis. The neurosis constitutes about a fourth of the total.

In from fifteen to twenty per cent of cases, gastric disturbances are attributable to disease of organs remote from the stomach, but only on infrequent occasions are such gastric disturbances the sole expression of an extragastric disorder. The most common location of disease in these cases is in the circulatory, pulmonary, nervous or urinary systems. Next in importance are diseases of dysfunction of the endocrine organs, deficiency diseases, toxic states induced by noxious gases, heavy metals, drugs, and inordinate use of tobacco and alcohol.

Complete and careful physical examination and a few well chosen laboratory tests will usually disclose the true nature of the condition.

Francis D. Murphy, Milwaukee.

McCOY, GEORGE W., AND HARDY, ALBERT V.

The Clinical Diagnosis of Amebic Dysentery. J. A. M. A., Vol. 107, p. 1357, Oct. 24, 1936.

The diagnosis of amebic dysentery is the most important point in handling the disease. Specific medication brings prompt and immediate relief, while symptomatic medication prolongs the condition and is hazardous to life.

Amebic dysentery must be considered an endemic disease which shows no predilection for any one area or any one class. Its incubation period varies from a few days to three months, but usually is one to three weeks. It must be considered in the differential diagnosis in all cases of enteric infection.

Clinically the disease usually is characterized by gastro-intestinal symptoms, but in some instances the invasion may be so mild that the entire picture is veiled. The more severe manifestations include evidences of an acute or chronic ulcerative process in the large bowel.

The onset of the disease varies. In 18 per cent of the 1,215 cases here reported, the onset was abrupt with symptoms other than diarrhea or abdominal pain. Fever and vomiting with abdominal pain localized in the right lower quadrant, and accompanied by tenderness and rigidity often served to limit attention to the appendix. Appendectomy in these cases resulted in death in 41 per cent of thirty-two cases. Rectal distress with bloody stools resulted in the diagnosis of hemorrhoids. Other cases were diagnosed malignancy because of the weakness, mild diarrhea and blood in the stools with a mass in the region of the cecum or colon on examination. Fever was found to be present in seventy per cent of the severer infections.

The errors in diagnosis were usually the acceptance of a nonetiologic diagnosis such as colitis or "dysentery." In fatal cases the erroneous diagnoses in order of frequency were malignancy, appendicitis, appendiceal abscess, sepsis in or near the gall bladder and in one case, hemorrhoids.

In the total series of 1,409 Chicago cases there were 98 deaths. The highest fatality rate being in the nonhotel cases which had progressed for months or years. In no instance is it known that a fatality resulted where an early diagnosis was made and specific therapy was used.

The diagnosis of amebic dysentery depends upon a more persistent effort to arrive at an etiological diagnosis of all diarrheal diseases, and the recognition of the fact that it is widespread in the United States and that its clinical manifestations vary widely.

Francis D. Murphy, Milwaukee.

KIRK, ROBERT C.

The Takata-Ara Test and Its Relation to Cirrhosis of the Liver. J. A. M. A., Vol. 107, pp. 1354-1357, Oct. 24, 1936.

Clinicians everywhere are anxious for a liver function test which is of definite diagnostic value. Because of this, this investigation of the Takata-Ara test was carried out.

This reaction was originally used by Takata to differentiate lobar from broncho-pneumonia. It is based upon the fact that when fluid from the chest of a patient with lobar pneumonia is added to a solution of sodium carbonate, mercury bichloride and acid fushsin, a precipitate of mercury oxysol occurs. This is believed to be due to a decreased stability of the serum proteins produced by an increase in the globulin fraction. Later Takata and Ara used it in differentiating syphilitic and miningitic central nervous system disease.

Jeyler recognized the fact that a protein shift in the blood was not peculiar to lobar pneumonia, but also was present in liver disease. He found that the test was positive in all advanced cases of cirrhosis and usually negative in all other diseases.

The method used was as follows: to a nine-tenths per cent solution of sodium chloride the patient's serum was added and many dilutions made, varying from 1:2 to 1:61. To these dilutions 0.25 c.c. of a ten per cent solution of sodium carbonate was added, followed by 0.15 c.c. of a five-tenths per cent mercury bichloride. The tubes were shaken and read in five minutes and again in twenty-four hours. A pearly flacculent precipitate filling at least one-fourth of any tube and a definite precipitate in any of the first four tubes was considered positive, all others negative.

Of 106 patients on whom the test was used, the following results were obtained. Cirrhosis of liver, 15 were positive and 6 were negative. Five of the fifteen positives were confirmed at autopsy. Congestive heart failure, 7 were positive and 7 were negative, four of each showing the presence or absence of liver damage at autopsy. Hepatitis, 2 were positive and 3 were negative; cholecystitis, 3 were negative; liver malignancy, 3 were positive and 2 were negative; abscess of liver, one was negative; congenital hemolytic jaundice, 2 were positive and 2 were negative; leukemia, one was positive and one was negative; tuberculosis, two were positive and two were negative; lobar pneumonia, one was positive and four negative; hyperthyroidism, four were negative; and normal livers showed 6 positive and 32 negative reactions.

The rationale of the test is not well understood, but the author comes to the conclusion that it is not diagnostic of cirrhosis of the liver, and that any disease which causes an elevation of the globulin level is likely to produce a positive reaction.

Francis D. Murphy, Milwaukee.

GOLDMAN, LEON.

Gross Hemorrhage from Peptic Ulcer. J. A. M. A., 107:1537, November 7, 1936.

Many physicians do not appreciate the potential dangers of bleeding from a peptic ulcer. Of 349 patients entering the San Francisco Hospital because of gross hemorrhage, 15 per cent died from hemorrhage or associated conditions: perforation of the ulcer, pneumonia, cerebral or cardiac thrombosis.

Ulcers of the stomach heal more readily than those of the duodenum, which bleed more readily. Fatal hemorrhage is usually caused by erosion of a large artery. Arteriosclerosis is an important influence on the incidence and mortality.

Recurrence of ulcer symptoms precedes hemorrhage. Nausea, vomiting of blood, tarry stools, fainting and shock occur. The blood pressure is an early guide to the severity of the hemorrhage. The patient's age and the presence of arteriosclerosis are important prognostic factors. The mortality has been reported high—from 14.5 per cent to 58 per cent.

In this study the mortality rate of patients with ulcer was 17 per cent, in-

creasing in direct proportion with the age of the patient. The average age of the patients who died was 54, and the greatest incidence was between 40 and 70. 70.6 per cent showed evidences of arteriosclerosis. There was an abrupt rise in mortality after the second hemorrhage, showing that the ulcer was intractable to medical treatment and that surgery was indicated.

The plan of treatment was as follows: (1) absolute rest, (2) morphine to insure mental and physical rest, (3) frequent determination of blood pressure, hemoglobin, and red blood cells, (4) nothing by mouth except alkaline powders, (5) no intravenous fluid except blood for several days, (6) blood transfusions, (7) coagulants and astringents have little effect, (8) gastric lavage only if there is an accumulation of blood clots. If the patient fails to respond to medical treatment early surgery is indicated.

Francis D. Murphy, Milwaukee.

EUSTERMAN, GEORGE B.

Diagnostic Aspects of Roentgenologically Negative Gastric Disorders. J. A. M. A., 107:1432, Oct. 31, 1936.

A negative roentgenologic report of the digestive tract, if skillfully done, eliminates ulcer of the stomach and duodenum, gastric carcinoma, pyloric and duodenal obstruction, duodenal lesions, and deformities caused by adhesions. These roentgenologically positive disorders cause about 1/5 of the cases of chronic dyspepsia at the Mayo Clinic. The roentgenologically negative diseases are classified as follows:

(1) Unrecognized roentgenologically positive gastric disorders. Gastric and duodenal ulcers and small carcinomatous ulcers may easily escape detection or be impossible to detect. Gastritis and diaphragmatic hernias are also very easy to miss in examination.

(2) Roentgenologically negative disorders of the stomach itself. This group includes the functional disturbances or neuroses, habit dyspepsias, constitutional inadequacy, some forms of gastritis, and gastric allergy. Neuroses are the most common, accounting for ¾ of the "stomach trouble" at the clinic. Some features which characterize gastric neuroses are: (1) long duration without complications, (2) symptoms variable in degree and location and frequently continuous, (3) lack of sequence characteristic of organic lesions, (4) diffuse pain, (5) symptoms lacking at night, (6) disorders following emotional stress, (7) physical disability out of proportion to the severity of the complaint, (8) other evidence of psychoneurosis or hysteria. A personal or family history of asthma, hay fever, uticaria or eczema makes allergic disease a possibility. The disturbance here is a spasm of the smooth musculature.

(3) Gastric disturbances resulting from disease of the abdominal viscera other than the stomach itself. 1/3 to 2/5 of the gastric disorders have their origin in the gall bladder, appendix, pancreas, liver, small bowel, colon, or such conditions as epigastric hernia or helminthiasis. Cholecystitis is the most common. Diseased appendix is not as important as formerly considered. Liver disease is diagnosed by icterus or anasarca or by hepatic function tests and roentgenographic examination of the esophagus. The pain due to pancreatitis is very hard to diagnose and distinguish from perforating ulcer, cholecystitis, diaphragmatic hernia, renal and colonic lesions, sciatica and lumbago, but increased activity of serum lipase is an efficient test for pancreatitis. Intestinal disorders must be diagnosed by inquiries into the past history if the pain is at the umbilical level or lower. Addison's

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disease, intestinal parasites, tuberculous peritonitis, retroperitoneal adenopathy, and disease of the lower thoracic vertebrae must also be excluded

(4) Gastric disturbances resulting from disease remote from the abdominal organs Disease of the circulatory, pulmonary, nervous, or urinary systems may give rise to gastric symptoms and must be carefully considered. Endocrine dysfunction, deficiency diseases (such as pernicious anemia) and toxic states are often important factors. Gastric disturbances are seldom the only manifestations of these disorders and careful laboratory investigation will usually reveal the true nature of the underlying cause.

Francis D. Murphy, Milwaukee.

JORDAN, SARA M.

A Review of the Gastric Ulcer Problem. J. A. M. A., 107:1451, Oct. 31, 1936.

119 cases in which a diagnosis of gastric ulcer was made on a reasonable basis were studied. The following questions arise in the treatment of gastric ulcer:

(1) Is the visualized lesion actually organic? Spasm, adhesions, cicatrization of an old lesion, and a loop of small intestine may be confusing since they may deform the contour of the stomach. Exploratory laparatomy is sometimes necessary to make the correct diagnosis but usually repeated fluoroscopic examinations with spot films and trial observations and treatment checked by radiological examinations are sufficient.

(2) Is it benign or malignant? The history is often not reliable. If the duration has been short and the symptoms not compatible with those of ulcer, malignancy is probable. A recent change in symptoms, absence of food relief, and frequency of vomiting and loss of appetite and weight without obstruction indicate malignancy. Analysis of the gastric contents is important because there is usually free hydrochloric acid with an ulcer and achlorhydria with cancer. Occult blood in the stools points toward carcinoma, but this test must be made carefully and over a long period of time. A healed lesion is not malignant. Prepyloric and posterior wall lesions heal slowly and tend to become malignant. In any doubtful case trial treatment should be given to determine reaction and a careful follow-up made.

(3) Is it healable by medical treatment or would surgical treatment be a more adequate insurance against recurrence or malignant degeneration? Operation should be done if there is suspected malignancy or if recurrence might lead to future malignancy. Uncontrollable distress is a surgical indication, but this rarely occurs except in a posterior wall lesion penetrating the pancreas. Surgical treatment is considered greater security against malignancy, but adequate follow-up evidence is not yet available.

(4) Is it necessary to guard against recurrence of the gastric ulcer as if it were distal to the pyloric sphincter? If patients who have had a gastric ulcer continue to live an "ulcer life" they are less prone to recurrences than those who consider themselves ulcer-proof. It is necessary to eat carefully, abstain from smoking or drinking and avoid fatigue and worry.

Francis D. Murphy, Milwaukee.

BOLES, RUSSELL S., AND CLARK, JEFFERSON H.

The Role of Alcohol in Cirrhosis of the Liver. J. A. M. A., Vol. 107, pp. 1200-1203, Oct. 10, 1936.

Cirrhosis of the liver is a fairly common chronic disease, presenting in its later stages a well recognized clinical and pathologic picture. In its early stages the clinical diagnosis is seldom evident and is based more on presumption than on fact.

The etiology of the condition is not known, but is believed to be due to

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various toxic agents, which cause a destruction of liver cells and a proliferation of connective tissue with ultimate fibrosis of the organ. Alcohol has for many years been considered the etiologic agent together with such conditions as syphilis, tuberculosis, diabetes, and acute infections.

Lately the status of alcohol as the etiologic agent has been disputed. Because of this, 4000 autopsies were studied from March, 1933 to1935, with especial reference to histologic evidence of cirrhosis in these cases, and the age, sex and race of the individuals. The relationship which alcohol, acute infections, syphilis, diabetes and tuberculosis bore to the disease was also studied.

Following their observations the authors present the following classifications as more accurate and descriptive:

1. Circulatory—occurring in cases of prolonged circulatory failure incident to advanced myocardial degeneration with red atrophy of the liver.
2. Degenerative—occurring as a result of degeneration and necrosis of liver cells and proliferation of fibrous tissue and bile ducts. This type is believed to be due to alcohol and other toxic agents.
3. Infectious—a low grade infection producing fibrous tissue in the periportal spaces.
4. Obstructive—believed to be due to an obstruction of the bile flow with increased fibrous tissue and bile duct proliferation.
5. Pigment—the deposition of abnormal pigment resulting in a histologic picture similar to the obstructive type.

The cases were grouped as follows: 1. All those regardless of history that presented definite or questionable histologic evidence of cirrhosis. 2. All cases in which the clinical history stated that the patient was addicted to alcohol. 3. Cases in which the liver weighed more than 2000 grams except in conditions not related to this study.

In the first group there were 243 cases or six per cent. Most of these were males, and only 84 or 35 per cent gave a history of alcoholism. Of all these cases only two were observed in children. Of this group 62 per cent were of the portal type and 70 per cent of these did not present any history of alcoholism; 34 cases were of the fatty type and 80 per cent of these had an alcoholic history; 33 cases were of the cardiac type of cirrhosis and 85 per cent of these were nonalcoholic; 18 cases of the infectious type with no alcoholic history; 8 cases of biliary cirrhosis of which 50 per cent were alcoholics. In all the cases no case of pigment cirrhosis was observed.

The 4000 cases were further studied to determine how many with an alcoholic history showed definite evidence of cirrhosis. Of 228 cases with an alcoholic history 24 per cent showed definite cirrhosis and 13 per cent showed fatty metamorphosis.

Of those cases in which the liver weighed over 2000 grams there were 151, seventy-five of which were alcoholic and seventy-six nonalcoholic. Of the alcoholic, 40 per cent had portal cirrhosis and eight cases showed fatty degeneration. Of the nonalcoholic, 39 per cent had portal cirrhosis and six cases showed fatty degeneration.

Concerning other etiological factors, 31 per cent gave a history of acute infections; 9 per cent had active pulmonary tuberculosis, 11 per cent had syphilis and diabetes was present in thirteen of the cases.

The above results indicate that cirrhosis is not caused by any one of the indicated agents. The author further believes that the term alcoholic cirrhosis be abandoned because the lesion occurs under a variety of conditions.

Francis D. Murphy, Milwaukee.

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WHITE, C. S., AND COLLINS, J. L.

Acute Mesenteric Adenitis. J. A. M. A., Vol. 107, pp. 1023-1025, Sept. 26, 1936.

Acute mesenteric adenitis has not been recognized by many as a distinct medical or surgical entity. The author has had sixteen cases during the years 1931 and 1935 which presented a history and symptomatology resembling that of appendicitis. At operation none of these cases presented the pathological findings of acute appendicitis. The outstanding pathological finding was an enlargement of the glands in the distal three feet of the mesentery of the small intestine, together with a small amount of peritoneal exudate and a moderate congestion of the cecum and small intestine.

The condition is characterized clinically by an onset of abdominal pain without previous history of any infection. This pain is generalized but more intense in the lower abdomen. The temperature is usually about 102 to 103 degrees Fahrenheit with pulse and respirations corresponding. Constipation is usually present, together with nausea, but vomiting only until the contents of the stomach are emptied.

Physical examination reveals a moderately distended abdomen with tenderness in the lower abdomen. The white count usually is between 8,000 and 14,000.

The etiology of the condition is not known, some men believing it to be tuberculous in nature and others that it is due to some intestinal disorder. The author suggests the possibility that it may be due to a virus, such as is believed to cause poliomyelitis or influenza. Sometimes the differential diagnosis between this condition and genuine acute appendicitis is very difficult or impossible. The higher fever, the general malaise before onset of pain as seen in the cases of adenitis at times may be helpful.

Francis D. Murphy, Milwaukee.

TAYLOR, FREDERICK.

"The Acute Gall Bladder." S. G. O., 63:298-307, Sept., 1936.

This comprehensive and convincing article offers further argument for the increasingly popular prompt surgical treatment of acute gall bladder disease. The classification of the cases into acute edematous, acute suppurative, and acute gangrenous, is entirely a pathological one. In considering the usual signs and symptoms, such a differentiation, clinically, is impractical, the most outstanding variance being seen in the total white count which averaged, respectively, 12,500, 15,200 and 20,000, with some definite overlapping. The underlying lesion in the acute gall bladder is a vascular one upon which an inflammatory or infectious process may be superimposed. The usual symptoms are discussed and the observations made that all the signs and symptoms need not be present to make the clinical diagnosis of an acute gall bladder.

The mortality analysis of operated cases is of greatest interest and importance. Patients operated upon within 48 hours and those two to five days after the acute onset showed approximately the same mortality, five per cent. Those operated upon five days or more after the acute onset showed a mortality of twenty-three per cent. When it is realized that these time intervals apply to the date of onset and not to the date of admission to the hospital, it will be seen that rather prompt surgical treatment is usually indicated. In all instances, however, time must be allowed for the preoperative intravenous glucose and fluid administration. Since over 90 per cent of the cases coming to operation show

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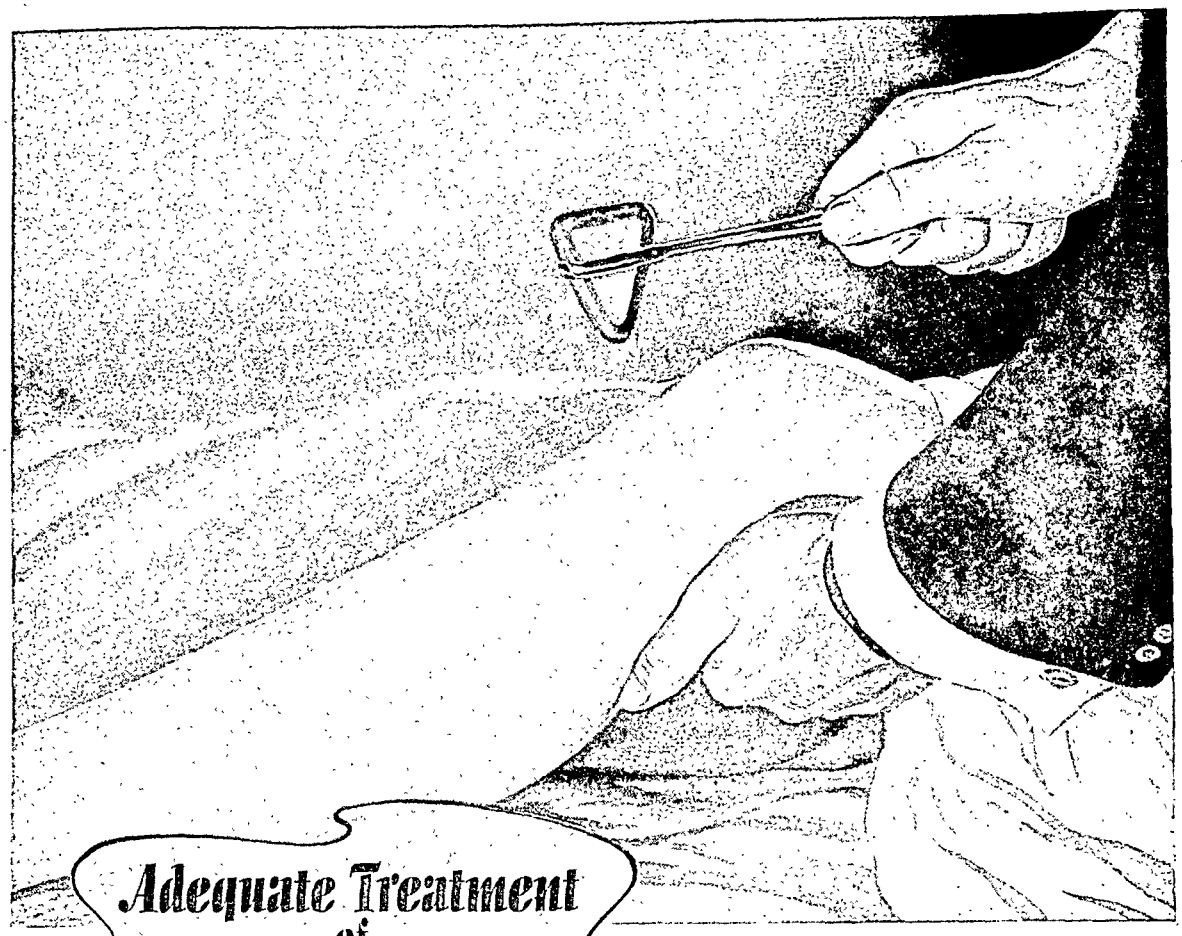
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stones in either the gall bladder or cystic duct, and since the majority of the patients have had previous symptoms, operation is, of course, the indicated treatment. The burden of proof rests upon those who advocate waiting for the acutely inflamed viscus to "cool"—during which time gangrene, perforation, extracholecystic abscesses or peritonitis may occur and the mortality rate greatly increase.

J. Duffy Hancock, Louisville.

EXPERIMENTAL PHYSIOLOGY

McGOVERN, F. H.

Primary Tularemic Ulcers in the Pharynx. J. A. M. A., 107:1629, Nov. 14, 1936.

The author presents the case of a woman, aged 32, married, who entered the hospital because of an extreme sore throat of twelve days duration. The onset had been sudden with chills and fever. It was later learned that she had picked ticks from her pet dog one week previous to the onset of the disease. Physical examination revealed a large confluent ulceration of the posterior wall of the pharynx. The cervical glands were bilaterally large and tender. The temperature was 102.4° F. on admission. The urine was normal. The white blood cell count was 21,000 with a marked shift to the left. Cultures were negative for diphtheria. A diagnosis of Vincent's angina was made and treated with arsphenamines and antimony and potassium tartrate with no results. The throat was sprayed with one per cent mercurochrome with marked relief of the symptoms. Because of the unusual course of the case agglutinations for typhoid tularemia, typhus, and undulant fever were done. The first report showed a four plus agglutination against Brucella abortus in a dilution 1:320 and two plus in 1:1280. A one plus agglutination was found against the B. tularense in a dilution of 1:640. Six days later the B. tularense agglutination was four plus in a dilution of 1:1280 and the Brucella abortus agglutination was three plus in a 1:20 dilution. The U.S.P.H.S. found an agglutination for B. tularense in dilution of 1:2560 and 1:5120. The patient was afibrile two days after admission and was discharged six days later. Two months later she was in excellent health.

Francis D. Murphy, Milwaukee.

GOLDMAN, L.

Gross Hemorrhage from Peptic Ulcer. J. A. M. A., 107:1537, Nov. 7, 1936.

Hemorrhage from peptic ulcer is considered by many physicians to be a comparatively rare cause of death. The record of pathologists, corners, and large city hospitals, however, do not confirm this idea.

At the San Francisco Hospital, of the 1,025 entries of 890 patients with peptic ulcer 348 or 38 per cent entered because of gross hemorrhage from a peptic ulcer. Of these 11.1 per cent died of exsanguination, while an additional 4.9 per cent died of conditions associated with the bleeding.

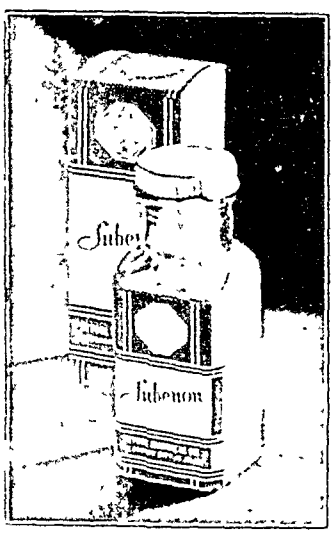
An ulcer which causes gross hemorrhage is necessarily active and progressive. If it is in the posterior wall of the duodenum and invades the retroduodenal and pancreatic tissue an inflammatory process is set up with the formation of adhesions which hold the ulcer open. The vessel most frequently involved in fatal cases is the superior pancreaticoduodenal or one of the coronary vessels of the lesser curvature of the stomach.

The symptom may appear suddenly in a patient with or without an ulcer history. The first symptom usually is nausea, followed by vomiting of blood.

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To Gastro-Enterologists

two new products deserving of your careful clinical consideration.



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SUBENON
for Arthritis

Two and one-half years have been spent in elevating the efficiency of this drug in all stages of every type of this disease. Now is the time to use this NEW method of attack on this age-old scourge.

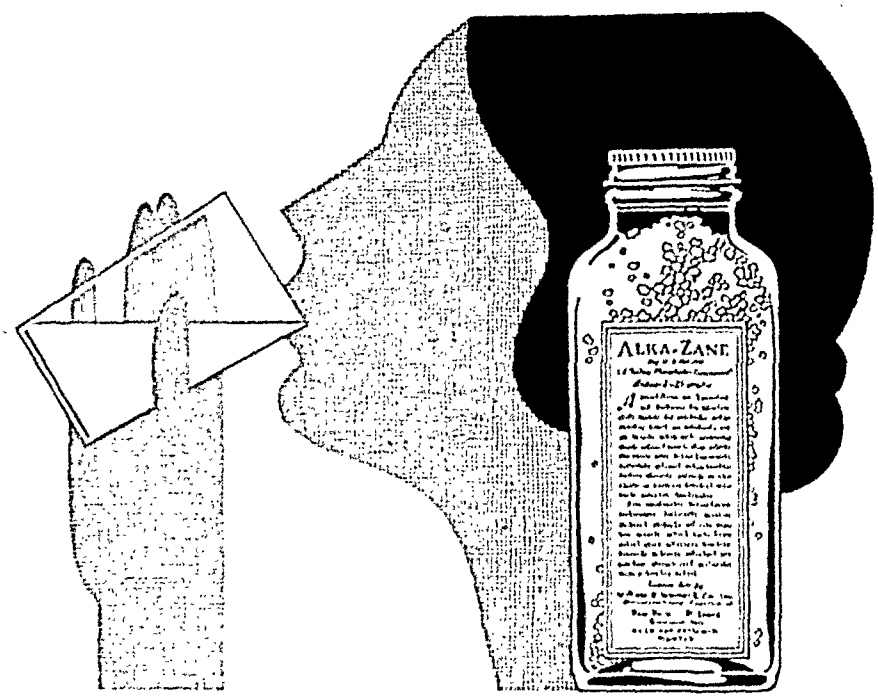
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ALKA-ZANE

The stools may or may not be tarry. This may be followed by shock if the hemorrhage is severe enough.

The percentage of cases of peptic ulcer which develop hemorrhage varies greatly. Various clinics find that from 19 to 31 per cent of the hospital cases develop hemorrhage and 10 per cent if outpatients are included.

The mortality also varies in different clinics being between 14.5 and 58 per cent. At the San Francisco Hospital the mortality, when complications of hemorrhage are included is 15 per cent. Two of the patients included in this series developed perforation after the hemorrhage. Most of these cases with hemorrhage were between 40 and 70 years, the average age being 54 years.

The successful treatment depends upon bed rest, sedation with morphine if necessary, blood transfusion and the withholding of food. Parenteral fluids should be withheld for the first 24 to 48 hours. Gastric lavage should be reserved from those patients in whom the stomach is distended by blood clots.

Those cases who continue to have severe hemorrhage or repeated hemorrhage require surgical intervention because a large vessel usually is eroded. The type of operation to be performed depends upon the operative findings. The vessels are usually ligated and in some cases an anastomosis is made between the stomach and the jejunum.

F. D. Murphy, Milwaukee.

FAULEY, G. B., AND IVY, A. C.

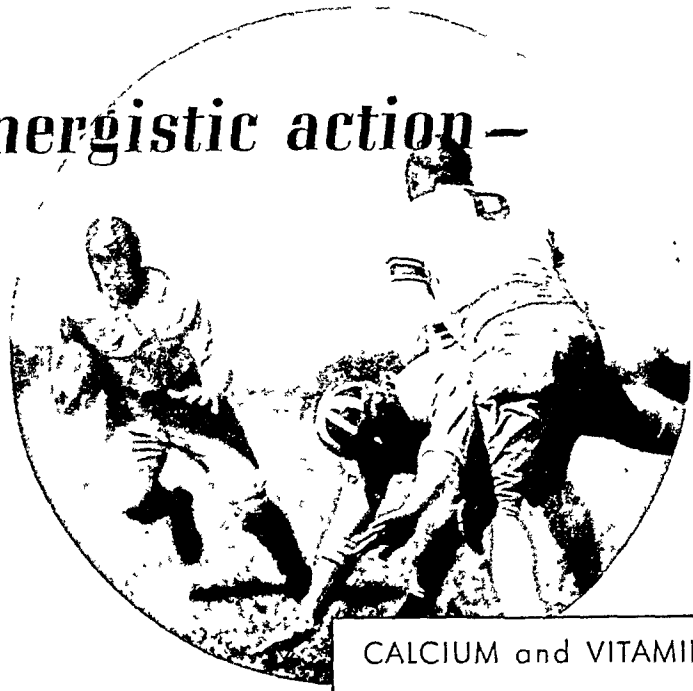
"The Prevention of Postoperative Jejunal Ulcers by Diet and Fundusectomy: An Experimental Study in Dogs." S. G. O., 63:717-724, Dec., 1936.

This work, all experimental on dogs, offers some conclusions that may prove to be of great clinical importance. The Mann-Williamson operation (gastrojejunostomy and drainage of bile and pancreatic juice into the last 15 centimeters of the ileum) invariably produces experimental ulcers analogous etiologically to postoperative jejunal ulcers in man.

When this operation was followed by the regular stock diet all the dogs died of ulcer within 17 weeks. If instead of the regular stock diet a special diet high in nuclear substances, vitamins and readily assimilable carbohydrates was used there was a marked delay in the development of the ulcer and the onset of fatal hemorrhage and perforation. However the dogs living longer than 20 weeks showed an ulcer incidence of 90 per cent.

Although the authors were convinced that fundusectomy does not produce a permanent lowering of the gastric acidity the two experiments just described were tried again on dogs which had been fundusectomized several weeks before a Mann-Wil-

Synergistic action—



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- IMPROVED APPETITE
- ROBUST HEALTH

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AXIOM—A good drainage (normal) stool - constipated stool + 70% water*

ARGUMENT—1. Constipated stools lack 70% water
2. Mucilose takes up 80% volumes water

SOLUTION—Constipated stool + (Mucilose + Water)** = good drainage (normal) stool

Q. E. D.—*Constipation corrected*

MUCILOSE

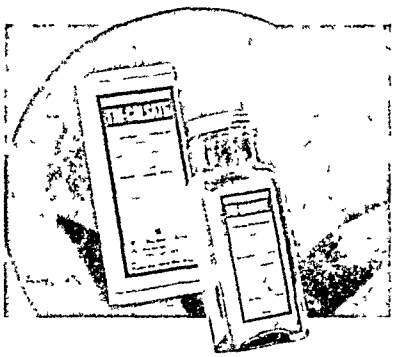
is a hemicellulose (vegetable gum) prepared by a special process from the Plantago loeflingii.

*Oelgoetz, A. W., Oelgoetz, P. A. and Wittekind, J., Am. J. of Dig. Dis. & Nutr., Vol. 3, p. 549, Oct. 1936.

**Ingested water and *not* water withdrawn from intestinal mucosa.

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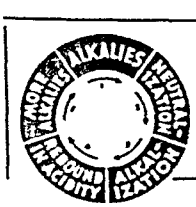
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liamson operation was done. Ulcer formation was observed in only three of eleven animals where there was fundusectomy, Mann-Williamson operation and regular stock diet. Of the thirteen animals having fundusectomy, Mann-Williamson operation and special diet none developed an ulcer although six lived longer than two years.

While there was not a great decrease in the total amount of acid in fundusectomized dogs one very interesting finding was observed. The average amount of gastric content at the end of four hours was only 40 per cent of that present in dogs where fundusectomy had not been done—in other words, the acid available for prolonged irritation of the jejunum was definitely less. This explanation may be of considerable significance.

J. Duffy Hancock, Louisville.

MONTGOMERY, M. F., AND STUART, J. S.
Studies on Secretion of Oral and Pharyngeal Mucous. Amer. Jour. Phys., 115, No. 3, May, 1936.

Studies were made on oral mucous and pharyngeal glands in regard to response to various stimuli, reflex response, and reaction to drugs; as compared to the salivary glands. Secretory response was estimated by direct observation of the glands and by collection of oral and pharyngeal secretion after eliminating the salivary supply, by means of esophageal fistulae. The mucous glands were observed to respond to nerve and drug stimulation in the same manner as the salivary glands. They do not secrete continuously, but only in response to conditioned and unconditioned reflexes. The mucous gland appear more responsive to mechanical stimulae than salivary glands. With exception of acid the mucous glands have a lower threshold of stimulation to taste and olfactory stimulae than the salivary glands. The mucous glands are less effected by water deprivation than the salivary glands as regards secretory rate.

I. S. Cherry, Chicago.

NUTRITION

SVIRBLEY, J. L.
The Effect of Diets and Various Substances on the Vitamin C Content of Some Organs of the Rat. Amer. Jour. Phys., 116, No. 2, 446-455.

Experimental study on rats was undertaken to obtain further data on the site of synthesis in the body of ascorbic acid and on the nature of its precursors. Rats were placed on various diets and after periods of time sacrificed and the organs analized for ascorbic acid by titration with indophenol indicator. The author found that under all conditions of diet the rats were able to synthesize their own vitamin C, however on vitamin B free diet the content of the organs in ascorbic acid was markedly reduced. Of the organs capable of synthesizing ascorbic acid only the liver and gut need be considered, their relative ability to form ascorbic acid apparently depending to some extent on the precursor in the diet, as shown by the relative concentrations of this vitamin in the organs. The vitamin C content of organs is decreased by nitrophenol, desiccated thyroid, and sodium fluoride and thyroid gland simultaneously administered in subminimal dosages. Vitamin C content of the liver is lowered by cincophen or ether administration. That the gut is the site of formation of ascorbic acid is suggested by the author because that substance is still synthesized in appreciable amounts after degenerative changes, and presumably disarrangement of hepatic function has been brought about by exposure to carbontetrachloride vapor.

I. S. Cherry, Chicago.

CLARKE, M. F., BASSIN, A. L., AND SMITH, A. H.
Skeletal Changes Due to Low Inorganic Salt Diet. Amer. Jour. Phys., 115, No. 3, 556-563, May, 1936.

Studies on bone of rats fed on low salt diets for various periods were undertaken to show relative variations in ash and fat free organic residues, moisture content and dimensions, between these and control rats qualifying in age, weight and caloric intake; and to correlate these if possible with breaking strength of the bone. Studies were continued further to determine if, on the exhibition of salt in the diet the bones of the deficient animals could approximate that of the controls. In these animals it was found that body weight ceased, but the long bones continued to increase slowly in length. The ash decreased and the moisture content of the bone increased during the salt free period. The proportion between ash and fat and moisture free organic residue became markedly distorted from that of the controls. Recovery on resuming salt was noted, but the percentage of moisture and ash as well as measurements failed to reach the age control values. Breaking strength appeared to depend more on structure as reflected in the size, rather than on the relative mineral content.

I. S. Cherry, Chicago.

THERAPEUTICS

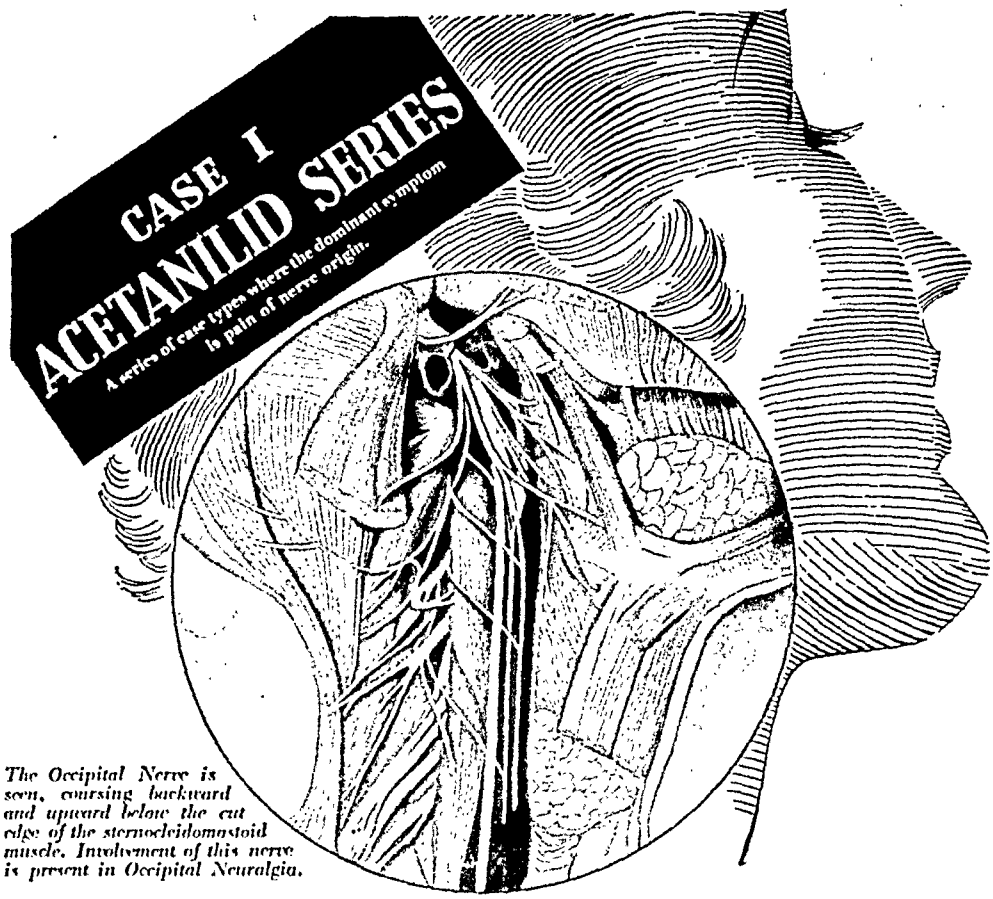
EADS, JOHN T.
The Use of Histidine Hydrochloride (Larostidin) in the Treatment of Peptic Ulcer. Ann. Int. Med., X, pp. 638-644, Nov., 1936.

This report deals with 85 cases of peptic ulcer (77 duodenal and 8 gastric ulcer) which have been treated with

CASE I

ACETANILID SERIES

A series of case types where the dominant symptom is pain of nerve origin.



The Occipital Nerve is seen, coursing backward and upward below the cut edge of the sternocleidomastoid muscle. Involvement of this nerve is present in Occipital Neuralgia.



OCCIPITAL NEURALGIA

CHIEF COMPLAINT: Paroxysmal pain with free intervals; tenderness of neck toward right ear.

HISTORY: Frequent colds; lack of energy; appetite poor; sleeplessness, and irritability.

PHYSICAL: Underweight; anemic; neurasthenic type.

SYMPTOMS: Hyperesthesia right cervical area midway between occiput and mastoid process.

DIAGNOSIS: Occipital neuralgia caused by exposure or infection.

TREATMENT: (Symptomatic) Acetanilid, 2-5 grains q. 4 hrs.

Bromo-Seltzer provides 3 to 3.5 grains of Acetanilid, plus its synergists—*Caffeine and Bromides—in each teaspoonful dose. Caffeine gently invigorates* the mental processes. Bromides promote relaxation of overwrought nerves. Citrates improve digestion, tend to replenish alkaline reserve and give to Bromo-Seltzer its effervescent palatability.

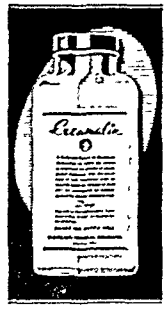
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"Pain disappeared after the first dose" is the significant comment of many clinicians in reporting their experiences with Creamalin therapy.

The ability of Creamalin to control pain and pylorospasm speedily is undoubtedly due to its unique astringent properties as well as to its rapid acid-fixing action. The special process employed in the preparation of Creamalin may well account for its unusual analgesic action. Try Creamalin and observe its rapid effect on pain.

The Creamalin Continuous Drip Treatment. Although Creamalin has yielded gratifying results in thousands of cases of peptic ulcer when administered orally, certain types of cases are more amenable to a form of treatment whereby diluted Creamalin is administered as a continuous drip. These cases include those 1) wherever a high nocturnal acidity renders the case refractory to intermittent oral treatment; 2) bleeding ulcers; 3) the generally refractory type. In one institution alone, 142 cases have been treated by the Creamalin Drip, and with one exception, x-ray findings were negative in from seven to ten days.

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daily intra-muscular injections of a 4 per cent solution of histidine hydrochloride. The number of injections varied from 15 to 36 with 70 cases receiving 24 injections each. These cases were followed up for periods ranging between six and eighteen months.

In the majority of the cases in which clinical improvement was manifest, it occurred early in the course of treatment, usually before five injections had been given; the poorest response occurred in those having 24 or more injections. A gain in weight, appetite, and sense of well-being accompanied clinical improvement but this tended to drop off during the follow-up period.

Patients presenting evidence of obstruction were not benefitted. Gastric ulcer patients yielded the best results both clinically and roentgenologically. Eight cases previously operated upon showed the quickest clinical improvement and five of these remained well after one year's observation. Likewise, those patients in the younger group, with shorter histories and no complicating factors such as obstruction or hemorrhage appeared to respond more quickly and more completely to the treatment.

Regarding the immediate results of histidine Eads could note no untoward reactions in any cases. Temperature, pulse, blood pressure and blood counts were unaffected. But only eight patients showed appreciable lessening in gastric acidity.

Eads concludes that the follow-up periods of from six months to 18 months in his 85 cases have shown that the favorable results obtained immediately during the active course of treatment with histidine hydrochloride are not continued in from 35 per cent to 65 per cent of his two groups of cases. His review of the literature in general supports this conclusion. For the average peptic ulcer patient Eads believes that the use of histidine alone offers less lasting beneficial end-results than does the regular orthodox medical treatment but that it might be worth trying in patients refractory to other regimens. The promptness with which subjective symptoms of pain and discomfort were allayed was noteworthy despite the failure to secure permanent relief. The mechanism by which histidine therapy produces benefit in those cases showing immediate improvement is, in Eads' judgment, by no means satisfactorily explained.

From a study of his own cases as well as from his review of the literature, Eads believes that histidine hydrochloride therapy cannot supplant the dietary-alkaline medical treatment.

B. B. Vincent Lyon and
C. F. Wirts, Jr., Philadelphia.

ABDOMINAL SURGERY

SHIER, R. V. B.

Large Bowel Obstruction. S. G. O., Vol. 63, No. 4, Oct., 1936.

Carcinoma of the large intestine, volvulus of the cecum or sigmoid, diverticulitis, and congenital or operative adhesions are the etiologic agents of large bowel obstruction. Stone in the kidney frequently produces symptoms simulating large bowel obstruction. The author bemoans the fact that only 15 per cent of the patients with large bowel obstruction consult a physician before it has advanced to a marked degree. A plea is made to treat the dehydrated, chronically poisoned patient, whose cellular structure is altered chemically and physiologically, before attacking the carcinoma. Treat the obstruction first, then the carcinoma.

To relieve the obstruction a cecostomy at a point removed from the ileocecal valve is made through a McBurney incision. After the bowel has been opened irrigations per rectum are started, and usually after 2-3 days through and through washings are made. The patient is fed and the toxic state corrected in from 10 to 14 days, after which the attack on the carcinoma may be made. The author prefers to have the patient out of bed for a few days before attempting the next stage.

If the hemoglobin is below 65 per cent a transfusion is given the night before, or immediately before the operation. An operative procedure adaptable to the particular growth found is made, and after two weeks the patients are allowed to get out of bed. Two months elapse before the cecostomy is closed.

The author feels that our next step forward in increasing the curability of carcinoma of the colon lies in getting the patients before the onset of partial obstruction.

Nelson Percy, Chicago.

HARKINS, HENRY N., HARMON, PAUL H., AND HUDSON, JEANNE E.

Peritonitis Due to Bile and to Liver Autolysis. J. A. M. A., Vol. 107, pp. 948-953, Sept. 19, 1936.

Bile peritonitis is a distinct clinical entity that is probably more common than has been realized. The etiology of this condition is not known, but has been supposed to be due to toxic action and anaerobic growth. The author in this instance wishes to advance the idea that secondary shock due to a decrease in the volume of the circulating fluid is an important lethal factor in this condition.

Peritonitis was produced in dogs by the intraperitoneal injection of ten per cent bile salt solution or whole gall bladder bile. This was followed by a gradual but profound lowering of blood

Gastric Ulcers Heal More Quickly...

and recurrences are less frequent when Irradiated Pet Milk is used in the diet.

The reasons — Pet milk is more easily digested than ordinary milk — less likely to cause intestinal irritation, and consequently conducive to early healing of affected areas.

It is sterile — completely and *surely* free from bacterial life — a positive safeguard against re-infection of healing tissues by milk.

Further recommending it strongly for use in cases of gastro-intestinal disorders are these additional qualities:

1. Uniformly rich in calories, furnishing twice the food value of ordinary milk.
2. Better balanced in nutritional elements than the usual milk and cream mixture.
3. Contains whey proteins so altered in character that they do not readily enter the blood stream in undigested form — an advantage in cases of milk sensitivity.
4. Enriched with vitamin D by exposure to ultra-violet rays — insuring more efficient utilization of calcium and phosphorus.
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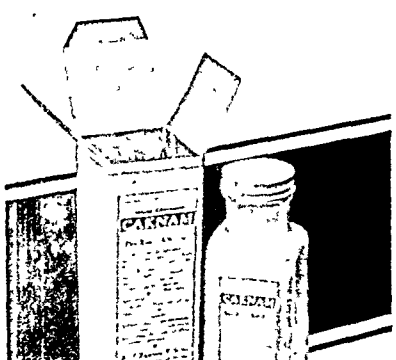
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pressure with a markedly lowered bleeding volume. In three cases the hemoglobin rose to 177, 178 and 190 per cent respectively. There was also an increase in the blood non protein nitrogen. As the peritonitis developed there was an enormous effusion of blood stained fluid into the peritoneal cavity. This fluid clotted spontaneously and was chemically similar to blood plasma.

Because of the aforementioned work it was thought that the secondary shock factor may be of importance in death due to intraperitoneal insertion of tissues. Experiments were therefore performed with this in mind. Liver and muscle were placed in the peritoneal cavity and subcutaneously. As a result of these experiments the following conclusions were reached. At least five lethal factors in experimental peritonitis due to bile or to implanted liver may be active; (a) local irritant action of the foreign substance producing plasma loss and secondary shock; (b) local damage to body tissues with absorption of toxic products produced; (c) action of absorbed products on general vascular permeability furthering secondary shock.

The plasma loss and secondary shock seem to be of more importance in death than any of the other factors.

Francis D. Murphy, Milwaukee.

SURGERY OF THE LOWER COLON AND RECTUM

RANKIN, FRED W.

"Concerning Colostomy." South. Med. Jour., 29:130-137, Feb., 1936.

In a well illustrated article, the Author gives an exceedingly practical discussion of colostomy, including an interesting historical sketch. The indications are two, one as a part of an extirpative (or palliative) procedure for cancer and the other as a decompressive measure for some benign obstruction such as imperforate anus or some benign inflammatory lesion such as diverticulitis. The two types of operation now used are first, the loop colostomy and second, the single-barreled or end colostomy. Three factors influencing the subsequent comfort of the patient and care of the openings seem important in the Author's experience. They are: first, taking all the slack out of the bowel so that it is pulled down from above as far as its mesenteric attachments will permit; second, bringing the bowel out through a small incision, usually a stab wound in the left groin; and third, bringing the lumen of the bowel (in a loop colostomy) entirely outside of the abdominal cavity. The site of the artificial anus may be varied, the usual locations being in the upper or middle portions of the low mid-line incision, at the site of the umbilicus which has been removed, or through a stab wound in the left groin, the latter location being favored by the Author. An elastic belt with a removable rubber section is preferred to any of the various cups, belts, etc., usually recommended. Sphincteric control of the new anus is declared to be impractical, the satisfactory care of the colostomy depending upon attention to diet and cleanliness of the stoma. Of great importance, too, is the attitude of the patient—and physicians and surgeons are urged to be less pessimistic in their discussion of this operation. It is a necessary procedure and one which is not incompatable with social and professional activities.

J. Duffy Hancock, Louisville.

COLLAR, FREDERICK A., AND RANSOM, HENRY K.

The One Stage Procedure of the Treatment of Carcinoma of the Rectum. Ann. Surg., 104:4, 636, 645.

Out of 270 cases of carcinoma of the rectum seen by the authors in the past six years, 221 accepted some kind of treatment. Fifty-one per cent of these were unsuitable for radical operation because of far advanced lesions or associated diseases. Palliative colostomy was done in 75 cases because it is considered of definit value. Seventy-two cases were treated by the one stage abdominoperineal procedure and 27 by the two stage procedure.

To the author's "it appeared that the second stage of this operation was as long and as difficult as the one stage operation and the mortality of the one stage procedure should not be higher because of operative trauma if the patient could be brought to operation in as good condition."

Emphasis is placed on preparation of the patient with weak saline purges, daily enemata, bed rest most of the time, low residue, high caloric diet with high fluid intake, and blood transfusion if indicated for anemia. Bactrogen (Steinberg) was used preoperatively or more recently at the time of operation. The average period of preparation was seven days.

The operative procedure follows the method of Miles and Rankin. A long free end of the proximal colon allows early opening of the bowel without danger of wound infection. The excess bowel is removed after the wound has healed. A spinal anesthetic consisting of 80 mg. of novocaine and 20 mg. of pantocaine is administered.

In spite of the fact that the prone position with the hips flexed gave better exposure for the perineal part of the procedure the authors chose the Sims position because a fall of blood pressure was too often encountered when the former position was employed.

Reviewer's Note:

The question of a one stage or a two stage operation must be answered by

Control gastric hyperacidity without the use of alkalies!

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ANTACID—ADSORBENT

Amphojel, Wyeth's Alumina Gel, is a creamy palatable colloidal suspension of hydrated alumina—$Al_2(OH)_6$—capable of neutralizing in one hour not less than 12 volumes of gastric juice containing 0.36% hydrochloric acid. Thus, a teaspoonful will *neutralize to Toepfer's reagent* over one and one-half fluid ounces of such juice or a corresponding amount of stronger secretion.

Even excessive use of Amphojel will not cause gastric alkalinity, altered pH of the blood stream or secondary acid rise.

Indicated for the control of gastric hyperacidity

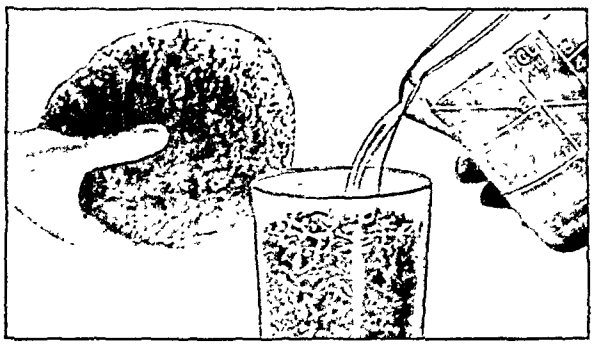
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This simple test shows how ALL-BRAN functions: fill a glass 4/5 full of ALL-BRAN. Pour water up to the brim of the glass. Soak 15 minutes, and drain off excess water. Feel the water-softened mass. It's much like a soft sponge. In fact, laboratory tests* show that ALL-BRAN absorbs at least twice its weight in water.

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The "bulk" in Kellogg's ALL-BRAN is much like that in leafy vegetables. But with many people, the "bulk" in fruits and vegetables is largely broken down in the system . . . and intestinal muscles get too little exercise. Gentle-acting ALL-BRAN fiber does not break down. So it is much more satisfactory.

ALL-BRAN may be served as a cereal, or cooked into appetizing muffins, breads, etc. It is sold by all grocers. Made by Kellogg in Battle Creek.

*Tests made by Samuel P. Sadtler & Son, Inc., Analytical Chemists, Philadelphia, Pa

Eat Kellogg's ALL-BRAN regularly for regularity



the surgeon who does the operation. The surgeon with less experience will do more two stage operations and the one stage operation will be carefully selected. Those who have more experience will find a larger number satisfactory for the one stage procedure but even among surgeons with wide experience the two stage operation will still have a place in poor risks. Some support of this contention may be deduced from the authors' statement that "in the one stage operation the difficulties of regulating the colostomy are superimposed upon a patient recovering from a severe operation." Perhaps the removal of this burden would swing the balance from failure to success in some bordering cases.

Wayne W. Flora, Chicago.

FELSEN, JOSEPH.

Acute and Chronic Bacillary Dysentery. Amer. Jour. Path., XII, 3, p. 395, May, 1936.

A study based primarily upon the Jersey City epidemic of bacillary dysentery of 1934 is presented. The author's main purpose has been (1) to stress the fact that acute bacillary dysentery is a systemic disease in which the pathological lesions are caused by one or more toxins affecting, as well, extraenteric organs; that the intestine alone need not bear the main brunt of the infection; and (2) that the late manifestations of the disease bear a very close relationship to non-specific ulcerative colitis.

It is believed that the intestinal lesions in the human are due to the excretion of the dysentery toxin, circulating in the blood stream, through the bowel wall. It is believed, too, that the toxin may be reabsorbed and repeat the cycle. The terminal ileum and colon seem to have a predilection for the toxin as the greater lesions are found there, although any portion of the bowel may be involved. An enteric and a neurotropic toxin have been isolated by Olitsky and Kligler. Clinical evidence exists which points to the presence of an arthritic and a myelotropic toxin also. The frequent association of labial herpes suggests, too, the presence of a virus. Examinations of the spinal fluid and the fluid from joints have failed to show the presence of microorganisms. In the chronic type of disease with arthritis, the acute dysentery infection having long before subsided, the joint involvement is probably due to a streptococcus or streptococcic toxin. The enterococcus is often recovered from the stools and other materials. A marked toxic granulocytopenia is at times observed. As the bone marrow in two cases coming to autopsy showed no evidence of deficiency in granulocyte formation, it was concluded the destruction of the leucocytes took place in the peripheral blood or in the vascular sinusoids of the bone marrow into which the granulocytes must migrate after their extravascular formation. Therefore the toxins of B. dysenteriae should be considered from the standpoint of selectivity as enteric, neurotropic, arthritic, and myelotropic. The Shiga-Kruse, Flexner, Hiss and Sonne-Duval strains all enter into the general picture.

The intestinal lesion in the acute dysentery begins as a definite hyperemia of the mucosa of large and small intestine with moderate edema and diffuse lymphoid hyperplasia of the solitary acuminate lymph nodules. Peyer's patches are similarly involved. The goblet cells pour out quantities of mucus, apparently for protection. On the second and third days blood oozes through the relatively intact epithelium. Superficial mucosal ulceration takes place—the lymph nodes become larger and central necrosis appears. The mild case usually does not extend beyond this stage. As the terminal ileum is severely affected patients have been on occasion operated upon for acute appendicitis—the mesenteric lymph nodes are then seen to be large, soft and pinkish in color. The acute stage usually subsides by the end of the third week. Continuing intestinal symptoms indicate chronicity and probably secondary non-specific intramural infection. The mucosa bleeds easily on examination, ulcers appear, and, as time goes on, the submucosa and deeper layers become involved, the

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wall thickened, haustration eliminated, pseudopolyposis may occur, etc.—the picture of chronic ulcerative colitis.

Follow up studies of cases of acute bacillary dysentery have shown that in some patients intestinal lesions persist long after the dysentery organism has disappeared from the feces. The longest period of observation was 4 years. In the Jersey City epidemic 122 cases out of a total of 210 hospitalized patients were examined 9 to 12 months after the acute attack; 18.8 per cent gave evidence of chronic ulcerative colitis. Epidemiological studies revealed definite contact and familial incidence in non-specific ulcerative colitis and a geographic distribution corresponding to that of bacillary dysentery. Positive agglutination titers against B. dysenteriae were obtained in 62 consecutive cases of non-specific ulcerative colitis, in 2 of non-specific granuloma, and in 14 cases of chronic distal ilcitis. Control studies of 300 serums showed diagnostic titers in 4.6 per cent.

The laboratory diagnosis depends upon: 1. fecal culture —the specific dysentery organism is often isolated only during the first week; 2. diagnostic fecal bacteriophage; and 3. agglutination titer. The second begins to appear in the feces and the agglutination titer to rise in the blood after this time.

The character and modification of the dysentery toxins suggest that to be effective therapeutically, a specific serum must be used within the first few days when the major intestinal lesions occur. It should be an anti-toxin effective against known toxins that have been properly standardized by biological methods. Active immunization must be directed chiefly against the secondary non-specific invaders.

N. W. Jones, Portland, Oregon.

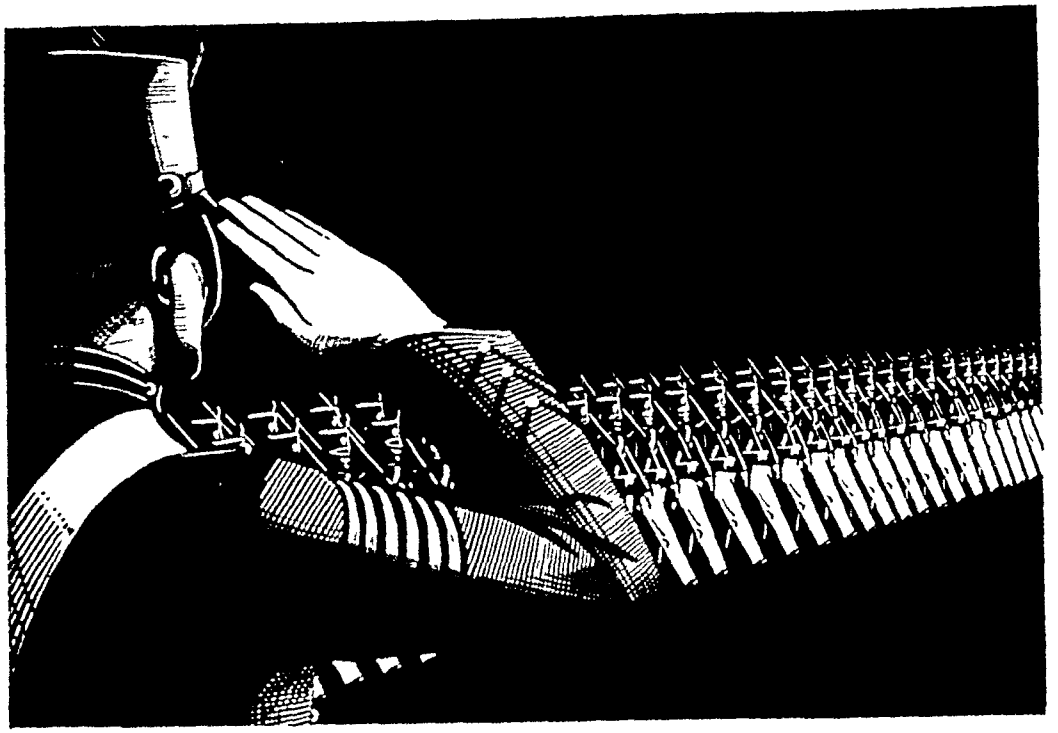
WOOLF, MONTAGUE S.

Operations for Cancer of Rectum. Amer. Jour. Surg., 35:1, 79-82, Jan., 1937.

In 1828 the first amputation of the rectum was done by an encircling incision around the anus, dissection close to the rectal wall and cutting across the bowel. The first advance was to remove the coccyx and suture the anus to prevent sepsis.

The first excision was planned by Sir James Paget in 1878. In 1884 Harrison Cripps reported three cases of perineal excision. In 1885 Kraska removed part of the sacrum but preserved the sphincter and pulled the bowel above the excision into the sacral wound. This operation was used almost universally for over 20 years.

By 1900 W. Ernest Miles was convinced that an abdomino perineal operation was necessary to remove the wide spread invasion in rectal growths. This operation gives the greatest insurance against recurrence but it is also the operation to which most patients succumb. W. J. Mayo, in 1912, reduced the mortality from 35% in the Miles type of operation to 13.3% by doing a single barrel colostomy and inverting the distal segment for later removal. Fatal sepsis often followed because of gangrene of the distal segment resulting from interference with its circulation. Coffey reported a 5% mortality with his quarantine drainage of the peritoneal space in which the dead segment of bowel lay. In 1915 D. Jones was able to remove more of the sigmoid from the perineal approach by freeing the sigmoid in the abdomen, being careful to preserve its blood supply, reconstructing the pelvic peritoneum at a higher level, doing a loop colostomy, and removing the rectum and sigmoid later. His mortality was 22%. Lockhart Mummery performs a loop colostomy then removes the rectum from the perineum by wide dissection after removal of the coccyx. His mortality in private cases is 3% and in charity cases it is 14%. Lahey makes a single barrel colostomy in the iliac region and implants the distal segment in the exploratory wound. Later the distal opening is closed and an abdomino perineal removal is done. This procedure allows for cleansing of the lower



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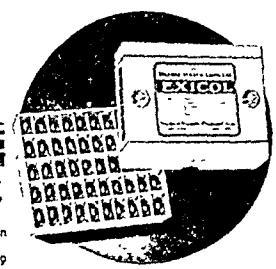
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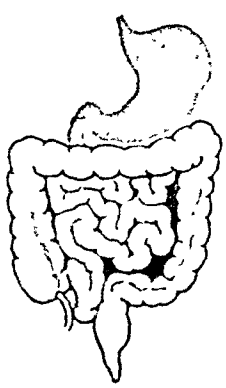
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*Am. J. Roentgen. 19:341, 1928. Am. J. Med. Scien. 6:187, 1931.
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segment but the abdomen is entered twice. Rankin and Gabriel perform a perineo abdominal operation, the first stage consisting of a loop colostomy and the second stage consisting of a perineal dissection and a placing of the rectum in the peritoneal cavity from which it is removed by an abdominal incision. Objections to this method are that two abdominal operations are required, accidental opening of the rectum would contaminate the peritoneal cavity, and the abdominal procedure is done late in the operation which might offer anesthetic difficulties especially with the use of "thecal analgesia."

Previous to 1926 these kind of cases were operated on by many staff surgeons and since then they have been operated on chiefly by one surgeon who is responsible for proctologic cases. Since the present arrangement has been in force the operative mortality has been reduced from 16.2% to 2.6%. In 38 operable cases the author reports a five year survival of 26% following the perineal resection of Mummery in comparison with a 21.7% five year survival in 46 cases resected previous to the organization of the proctologic service.

The operations used by the author are colostomy followed by posterior resection and the one stage abdomino perineal. The latter operation has not yet been used to its fullest value.

Wayne W. Flora, Chicago.

BRINALEY, G. V.

Carcinoma of the Rectum. J. A. M. A., Vol. 108, pp. 37-43, Jan. 2, 1937.

Practically all patients with carcinoma of the rectum can be cured if the diagnosis is made early enough and the proper surgical procedures carried out. The diagnosis is comparatively easy when the proper methods are used.

The prognosis after diagnosis depends upon the extent of the lesion. The length of time that a rectal carcinoma remains localized after the onset of symptoms varies from six to eighteen months, averaging 9.4 months. Extension occurs by direct continuity with other tissues, by lymphatic invasion and occasionally through the blood stream. The symptoms and signs of the disease are melena, a mild rectal discomfort, characterized by a feeling of heaviness, soreness or a mild cramping. Intense pain is practically never an early manifestation of the disease. In some cases there is a change in the bowel habit. Digital and proctoscopic examination usually aid materially in the diagnosis.

Statistics show that the degree of malignancy of rectal neoplasms are of grades one or two in approximately 50 to 75 per cent of the cases. The type of operation to be performed depends upon the degree of malignancy. More radical surgery should be performed for the lower grades of malignancy than the higher grades, even though the former appeared to be more advanced. Neoplasms of a highly malignant degree and of the borderline operability are treated preferably by radium and roentgen rays rather than by surgery. Lesions that are moveable or which have not metastasized to the regional lymph glands are definitely better risks. In addition, the sex, the age and the general physical condition influences the prognosis and the type of surgery to be performed. The mortality rate in the male is higher than in the female because of the smaller and therefore less accessible pelvis and the fact that the pelvic peritoneum is less resistant in the male.

The author believes that a graded operation divided into two or more stages is usually preferable. Most cases require an abdominoperineal resection in two stages, but some only require an abdominal approach. The author also believes that the electrocautery knife should be used in almost all cases. X-ray and radium treatment he believes should be reserved for inoperable cases and those who refuse operation.

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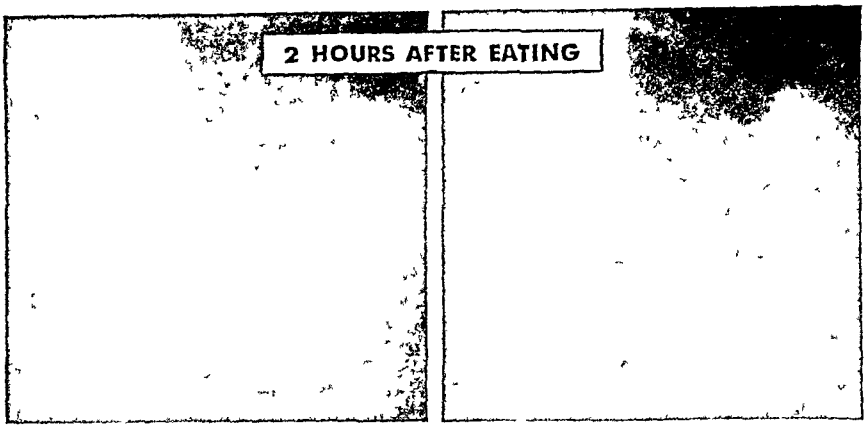


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Phosphorus	0.620	0.392	0.125	0.093	0.093	0.180
Copper	0.0013	0.0005	0.00017	0.00034	0.000015	0.00023
Vitamin B (B_1)	+ + +	+ +	— to +	+	+ +	+ to + +
Vitamin G	+ + +	+	— to +	+	+ + +	+ + +
Moisture	7.0	8.0	10.9	35.3	87.0	73.7
Protein	15.0	15.2	11.0	9.2	3.3	13.4
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DIGESTIVE DISEASES and NUTRITION

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